The American Journal of

DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

Volume 18 December, 1951 Number 12

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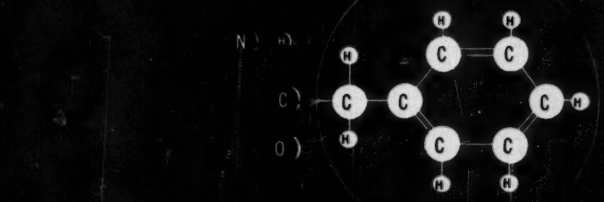

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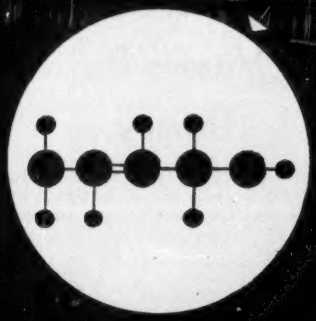

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Pyridoxine Hydrochloride	3 mg.
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Vitamin B_{12}	30 mcg.
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*MDR—Minimum Daily Requirement
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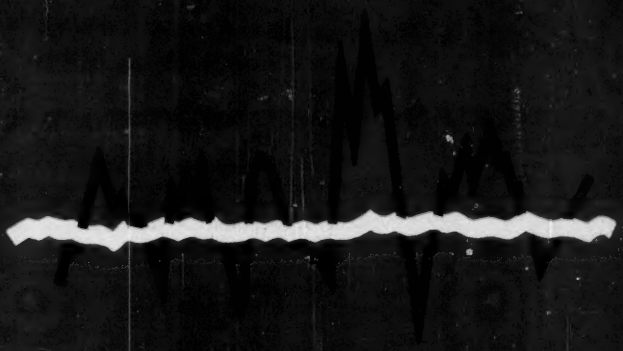

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*Peptic Ulcer. A. C. Ivy, M. I. Grossman and W. H. Bachrach, Blakiston Publishing Co., Phila., 1950.

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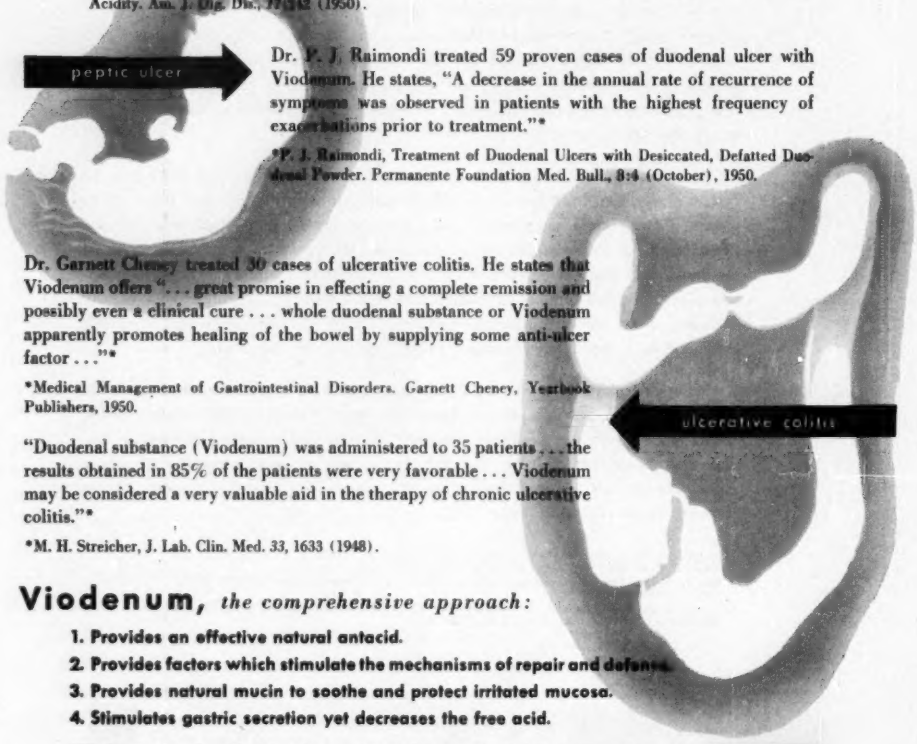
*S. Krasnow, F. Steigmann and L. L. Hardt, Comparison of Effectiveness of Various Antacids on Gastric Acidity. Am. J. Dig. Dis., 17:142 (1950).



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*P. J. Raimondi, Treatment of Duodenal Ulcers with Desiccated, Defatted Duodenal Powder. Permanente Foundation Med. Bull., 8:4 (October), 1950.

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*Medical Management of Gastrointestinal Disorders. Garnett Cheney, Yearbook Publishers, 1950.

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*M. H. Streicher, J. Lab. Clin. Med. *33*, 1633 (1948).

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DIABETES MELLITUS AND CONCOMITANT LEUKEMIA

JEROME T. PAUL, M. D., WILLIAM R. BEST, M. D., AND LOUIS R. LIMARZI, M. D. Chicago, Illinois.

REPORTS OF DIABETES mellitus and concomitant leukemia are infrequent. Rebitzer (1) in 1892 recorded the first instance of the association of the two diseases. Since then, sixteen additional cases (2-10) have been described. Joslin (10) observed eight cases of leukemia in a series of 29,000 diabetics. During the past seventeen years we have had the opportunity to study 805 cases of leukemia. Of this group 675 were studied at the Illinois Research Hospital and the Hematology Clinic of the hospital and 130 were admitted to the St. Francis Hospital, Evanston, Illinois. Ten cases of coexistent diabetes mellitus and leukemia were noted.

CASE STUDIES

A. A., a 62 year old white male, was first seen on December 10, 1948. Symptoms at this time included weakness and fatigue of two years duration, a twenty pound weight loss during the past two years, swelling of the ankles and legs and numbness of the toes. Patient was a known diabetic of at least three years duration and had been well controlled on a diet of 2300 calories with 185 grams of carbohydrate and a daily dose of 20 units of protamine-zinc insulin and 10 units of unmodified insulin as a mixture. Physical examination revealed palpable adenopathy in the cervical, axillary and inguinal regions and an enlarged spleen and liver. Blood counts on December 10th were as follows: hemoglobin 6.2 grams, erythrocytes 2,300,000, leucocytes 45,000, lymphocytes 97%, myelocytes 1% and neutrophils 2%. The patient was seen in the hematology clinic where the diagnosis of chronic lymphatic leukemia was confirmed and he was placed on urethane therapy. During the next two weeks the erythrocyte count had dropped to 1,640,000. Because of pronounced weakness and difficulty in walking, he was admitted to the hospital on January 1, 1949. Physical examination on admission revealed an acutely ill, pale white male in a semi-stuporous state. The temperature was 105°, pulse 100 and respirations 30. A blood transfusion was started but discontinued because of a chill. He expired two days after admission. Autopsy findings were those typical of a chronic lymphatic leukemia.

D. P., a 35 year old colored female, was first seen on August 21, 1939. At that time she complained of fatigue and weakness of two months duration. Two years prior to this she was advised to restrict the carbohydrates in her diet following the onset of polydipsia and polyuria. A glucose tolerance test revealed a fasting blood sugar of 333, one-half hour later 400, and one hour later a blood sugar of 500 was obtained. All urine specimens contained four plus sugar. The patient was adequately controlled on a 1800 calorie diet with 150 grams of carbohydrate. Hematological work-up on August 21, 1939 was as follows: hemoglobin 11 grams, erythrocytes 3,770,000, leucocytes 226,000 and reticulocytes 0.1%. The peripheral blood smear included myeloblasts 2%, promyelocytes 3%, myelocytes 17%, metamyelocytes 23%, stab forms 30% neutrophils 20%, eosinophils 1%, basophiles 1% and lymphocytes 3%. Smears of the aspirated sternal bone marrow were characteristic of chronic myeloid leukemia. X-ray therapy, in the amount of 850 roentgen units was administered from August 26, 1939 to February 20, 1940. On October 4, 1939 the white blood count was 77,000 and on December 6, 1939 the leucocytes numbered 8,800. She died July 8, 1940 at home.

J. S., a 71 year old white male, was first seen on April 24, 1945. Patient was well until November 1944 at which time he noted weakness and pruritus of the skin, of the face and anterior chest. During this six month period he lost seventy-five pounds in weight. Physical examination revealed bilateral palpable axillary nodes, an enlarged spleen extending to the middle and down to the left iliac crest, an enlarged liver and systolic murmurs over the apical and aortic areas of the heart. Urinalyses showed an occasional trace to one plus test for sugar. The glucose tolerance test was reported as follows: fasting blood sugar 122, one-half hour later 157 and one hour later 222. Hematological work-up included a hemoglobin of 9 grams, erythrocytes 3,100,000 and leucocytes 540,000. The peripheral blood smear showed lymphoblasts and atypical forms 15%, lymphocytes 80%, stab forms 1%, neutrophils 2%, eosinophils 1% and basophiles 1%. A marked lymphocytic infiltration was found on examination of the aspirated sternal bone marrow. Patient moved elsewhere, where he died September 12, 1946.

M. S., a 48 year old white female, was first hospitalized in May, 1938, for an acute episode of weakness, dizziness and excessive perspiration of one week duration. In 1931 a diagnosis of diabetes mellitus had been established and she had been taking 30 units of unmodified insulin since. Laboratory examination revealed a leucocyte count of 14,200, blood sugar of 200 and urinary glucose varying from negative to four plus on fractional tests. One year later she was readmitted because of bilateral glaucoma. While convalescing from eye surgery, she developed fever and diarrhea. The diarrhea was controlled by sulfa drugs and symptomatic measures. Adequate diabetic management was obtained by use of 20 to 40 units of unmodified insulin daily and a 1500 calorie diet. Because of a leucocyte count of 100,000 during June 1939 a sternal aspiration was done. The bone marrow showed a nucleated cell layer of 52% (concentrated method). The marrow smears were characteristic of chronic myeloid leukemia. The patient was admitted for the third time in August 1941. She had lost forty pounds in three months and complained of enlarged, sore glands in the neck. Examination revealed palpable cervical axillary and inguinal adenopathy, an enlarged spleen and a palpable liver. Blood counts were as follows: hemoglobin 55%, erythrocytes 3,200,000, leucocytes 355,000. The peripheral blood smear included blast cells 37%, promyelocytes 13%, myelocytes 21%, metamyelocytes 9%, neutrophils 8%, basophils 9%, esinophils 1% and lymphocytes 2%. The blood sugar was 270 and the urinalysis showed four plus tests for sugar and acetone. She was placed on a six hour schedule and the dose of protamine and unmodified insulin was gradually increased. The patient became progressively worse and expired seven days after admission.

N. E., a 51 year old white female, was first seen on September 22, 1948. She had been a patient at the Elgin State Hospital since July, 1948. On admission to this hospital in July, the leucocyte count was determined to be 90,000. A diagnosis of mild diabetes mellitus was also established. The glucose tolerance test revealed the following: fasting blood sugar 148, one-half hour later 180, one hour later 225. Physical examination included the residuals of a left hemiplegia, bilateral palpable axillary nodes and a palpable spleen. Hematology work-up on September 22, 1948 was as follows: hemoglobin 13.6 grams, erythrocytes 5,030,000 and leucocytes 70,000. The peripheral blood smear included myeloblasts 2%, leukoblasts 13%, myelocytes 25%, metamyelocytes 18%, neutrophils 25%, basophils 5%, monocytes 4% and lymphocytes 8%. Sternal marrow studies confirmed the diagnosis of chronic myeloid leukemia. The patient was placed on urethane therapy, three grams daily. Later the dose was reduced to one gram daily. During the period from October 1948 to April 1949 the leucocyte count varied from 31,500 to 11,500.

D. C., a 72 year old white male, was first seen on July 30, 1936. Patient was a known diabetic of ten years duration and had been controlled on a 2000 calorie diet containing 120 grams of carbohydrate. He entered the hospital because of an ulceration on the lower left leg which developed following trauma to the leg. On examination the spleen was found to be enlarged. Blood counts were as follows: hemoglobin 75%, erythrocytes 4,160,000, leucocytes 123,200, lymphocytes 96% and neutrophils 4%. A diagnosis of chronic lymphatic leu-

From the Department of Medicine, The University of Illinois, College of Medicine, Chicago, Illinois and St. Francis Hospital, Evanston, Illinois.

Aided by a Grant from Armour and Company, Chicago, Illinois.

Submitted June 18, 1951.

kemia was made and x-ray therapy to the spleen administered. The patient was readmitted to the hospital on April 13, 1937. Symptoms at this time included weight loss, weakness, cough, polydipsia and polyuria. Examination disclosed many moist rales over the lung bases and the spleen was palpable four fingers below the left costal margin. On admission the fasting blood sugar was 222 and the blood counts showed hemoglobin 75%, erythrocytes 3,840,000, leucocytes 44,500, lymphocytes 64%, neutrophils 34% and monocytes 2%. The patient's course was progressively downhill, he became stuporous and expired the day after admission.

The patient was readmitted to the hospital on September 1, 1949 for regulation of the diabetes. The physical examination was essentially negative except for the finding of an elevated blood pressure (190/100). Blood counts on September 2, 1949 were as follows: hemoglobin 12.8 grams, erythrocytes 4,100,000, leucocytes 49,200, lymphocytes 91%, stab forms 1%, and neutrophils 8%. She was discharged on 30 units of protamine zinc insulin daily. The fasting blood sugar was 131 on this management.

M. L., a 59 year old white female, was first hospitalized in January 1934 at which time a hysterectomy was performed.

TABLE 1

Case	Sex	Age	Race	Type of Leukemia	Initial White Blood Count	Duration of Diabetes Prior to Onset of Leukemia	Duration of Life after Onset of Leukemia	Insulin Dosage (units)
A.A.	M	62	W	Chronic Lymphatic	45,000	1 year	2 years	20 Protamine-Zinc 10 Regular
D.P.	F	35	C	Chronic Myeloid	226,000	2 years	13 months	None
J.S.	M	71	W	Chronic Lymphatic	540,000	Diagnosed same time	23 months	None
M.S.	F	48	W	Chronic Myeloid	100,000	8 years	26 months	20-40 Regular
N.E.	F	51	W	Chronic Myeloid	90,000	Diagnosed same time	18 months	None
D.C.	M	72	W	Chronic Lymphatic	123,200	10 years	9 months	None
E.B.	F	54	W	Chronic Lymphatic	34,900	2 years	Unknown	10 Protamine-Zinc
G.C.	F	60	W	Chronic Lymphatic	48,300	9 years	Unknown	25 Protamine-Zinc
M.I.	F	59	W	Chronic Lymphatic	12,950	½ year	Living	20 Protamine-Zinc
A.O.	F	55	W	Subacute Lymphatic	19,500	2 years	1½ months	30 Protamine-Zinc 10 Regular

E. B., a 54-year-old female, was first seen on November 29, 1948. Diabetes mellitus was known to have existed since 1946. She had been taking ten units of protamine-zinc insulin prior to admission. In September 1948 she noted blurred vision, dysuria, polyuria and pruritus vulvae. Physical examination revealed bilateral cervical adenopathy, deep punctate exudates in the fundi, blood pressure of 210/130 and a systolic murmur over the aortic area of the heart. Albumin and sugar were found on repeated examinations of the urine. On admission to the hospital the fasting blood sugar was 295. Adequate control was maintained by the use of thirty units of unmodified insulin before breakfast and fifteen units before the evening meal. Blood counts on December 1, 1948 showed the following: hemoglobin 13.6 grams, erythrocytes 3,800,000, leucocytes 34,900, lymphocytes 81%, neutrophils 17% and eosinophils 2%.

G. C., a 60 year old white female, was first hospitalized on June 16, 1947. The patient had been a known diabetic since 1938. Glycosuria was controlled by diet and insulin. A "hacking" cough developed about three weeks prior to admission and an x-ray of the chest revealed a lobar type of pneumonia involving the upper left lung. A fasting blood sugar of 136 was obtained on a diet of 1800 calories with 125 grams of carbohydrate and 25 units of protamine zinc insulin daily. Blood counts on June 16, 1947 showed the following: hemoglobin 14.5 grams, erythrocytes 4,120,000 and leucocytes 48,300. The peripheral blood smear included lymphocytes 82% and neutrophils 18%. Smears of the aspirated sternal bone marrow showed a marked lymphocytic infiltration consistent with chronic lymphatic leukemia.

She was readmitted on April 1944 because of some increase in the size of the hands, nose and jaw. The patient entered the hospital for the third time in August 1948. Some progression in the acromegaly was noted and x-rays of the skull showed an enlargement of the sella turcica. On the fourth admission in May 1929 an elevated blood pressure and diabetes mellitus was found in addition to the acromegaly. The diabetes was controlled by diet and a daily dose of 20 units of protamine-zinc insulin. In November 1949 she became aware of a number of enlarged nodes in the neck, axilla and inguinal regions. She entered the hospital again on February 10, 1950. Principal complaints at this time included progressive fatigue and a twelve pound weight loss during the past month. Physical examination revealed acromegalic features of the face and hands, bilateral palpable cervical and axillary adenopathy, an enlarged spleen and blood pressure of 140/80. On admission the fasting blood sugar was 148. Blood counts on February 11, 1950 were as follows: hemoglobin 11.0 grams, erythrocytes 3,810,000, leucocytes 12,950, lymphocytes 69%, neutrophils 25%, eosinophils 2% and monocytes 4%. The aspirated sternal marrow was hypercellular with a marked lymphocytosis. Approximately 70% of the cells were lymphocytes.

A. O., a 55-year-old white female was first hospitalized on December 11, 1943, because of a chronic ulcer of the left foot. Urinalysis revealed a positive test for sugar and the fasting blood sugar was found to be 180. Blood counts at this time were essentially normal. The diabetic state was controlled by a 2000 calorie diet and a dose of 50 units of protamine-zinc insulin and 20 units of unmodified insulin. She

was readmitted on January 7, 1945, following development of a discolored area of the skin of the right, large and second toes. On admission, the fasting blood sugar was 258 and the blood counts revealed hemoglobin 13.0 grams, erythrocytes 4,340,000 and leucocytes 8,500. The patient was admitted to the hospital for the third time on December 4, 1945. Nausea and vomiting had begun two days previously and she was brought to the hospital in a stuporous state. Physical examination revealed bilateral cervical and inguinal adenopathy, a large hard spleen and a palpable liver. The fasting blood sugar was found to be 285. Blood counts were as follows: hemoglobin 8.0 grams, erythrocytes 2,490,000 and leucocytes 19,500. The peripheral blood smear included blast cells 27%, lymphocytes 41%, neutrophils 26%, stab forms 1%. eosinophils 2% and monocytes 3%. The blast cells were lymphoid in type. Blast cells, similar to those in the peripheral blood, predominated in the sternal marrow. On the basis of the clinical findings and the hematological picture, a diagnosis of subacute lymphatic leukemia was made. On January 14, 1946 the leucocyte count was determined at 52,000. The diabetes was controlled by a daily dose of 30 units of protamine-zinc insulin and 10 units of unmodified insulin. Three blood transfusions were administered but she continued to fail and expired on January 15, 1946.

DISCUSSION

Of the seventeen cases of coexistent diabetes and leukemia recorded in the literature eight were of the myeloid type, seven lymphatic and one was monocytic. Twelve cases were known to have been diabetic prior to the development of leukemia. The time of onset of diabetes or leukemia was not definitely established in the remaining five patients. Eleven of the patients were fifty years of age or older and males predominated eleven to six.

Our group of ten cases of diabetes and leukemia consisted of seven females and three males. Eight of the patients were fifty or more years of age. The types of leukemia represented were as follows: six cases of chronic lymphatic, three cases of chronic myeloid and one case of subacute lymphatic. Diabetes mellitus was known to have existed prior to the onset of leukemia in eight cases. In two cases the diagnosis of diabetes and leukemia was established at the same time.

The diabetic state did not seem to affect the course of leukemia. Two patients survived for two years after the diagnosis of leukemia was made and three patients were known to be alive one year later.

SUMMARY

The association of diabetes mellitus and leukemia in the same patient is infrequent. Ten cases of coexistence of these two diseases are reported. This group is part of a series of 805 cases of leukemia studied.

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ACHYLIA GASTRICA: KEYSTONE IN THE DEVELOPMENT AND ERADICATION OF MACROCYTIC ACHYLIC ANEMIA (PERNICIOUS ANEMIA, ADDISON-BIERMER).

FREDERICK S. WEINBERG, M. D. New York, N. Y.

TODAY, ACHLORHYDRIA, anacidity and achylia gastrica are regarded as synonymous, and the terms are used interchangeably. It is the assumption that these three names define the same clinical conditions: Lack of hydrochloric acid in the gastric juice. Achylia gastrica, in addition, supposedly implies the absence of pepsin and ferments. For clinical purposes this distinction shall be of no significant importance.

Since there are apparently different forms of 'lack of hydrochloric acid', one has been forced to introduce a division among achlorhydria, anacidity and achylia gastrica as to 'true' and 'false' conditions; thus, each writer has to explain what he wishes understood by his use of a particular expression.

Submitted June 21, 1951.

Up to now we have found an unbelievable number of names in medical literature for what has been apparently considered the same condition: Idiopathic achlorhydria, achlorhydria constitutionalis (Schmidt); achylia gastrica simplex (Martius); achylia gastrica constitutionalis (Schmidt); pseudo-achylia gastrica (Henning); unexplained achylia gastrica (Bloomfield and Polland); histamine refractory achylia gastrica, apparent achylia gastrica (Bockus); partial achylia gastrica (Forsgreen); esential achlorhydria (Winkelstein), and more.

One has been led to believe that the introduction of the fractional gastric test with histamine stimulation has brought about a clearing up between the abovementioned *'true'* and *'false'* conditions. The claim is

that we can speak of a 'true' achlorhydria, anacidity or achylia gastrica only when at no time during digestion is free hydrochloric acid found by means of the fractional alcohol method and histamine injection. The 'false' condition exists when the gastric contents show no free hydrochloric acid with the Boas-Ewald test meal, or with fractional withdrawal, but when, after histamine injection, free hydrochloric acid will be found.

Henning, however, has seen in many cases of histamine refractory achlorhydria the proof become positive some time later, and Faber writes that in complete anacidity, and even in histamine refractory cases, it is by no means unusual for the acid secretion to return. Therefore, Henning and Norpoth make this appraisal: "Is the histamine test able to differentiate between the functional achylia gastrica and the organic one?" They conclude that the different forms of achylia gastrica cannot be distinguished by the alcohol-histamine test.

Of what value, then, for the diagnosis of achylia gastrica is the fractional alcohol test with histamine injection? So Bockus is seemingly refuted in his opinion that all diagnoses of achylia gastrica *before* the introduction of the fractional gastric analysis and, more particularly, *before* the use of histamine must be discarded.

Of course this was a very singular point of view, because achylia gastrica was discovered and diagnosed incontestably before the introduction of these tests; we can say, in fact, that all the important papers about achylia gastrica were written *before* these tests were used. I will venture further by stating that, in my opinion, with the advent of the fractional alcohol and histamine tests, our previous knowledge of achylia gastrica has today been set aside as inapplicable and the present confusion has come about. The abundance of terms alone is a clear sign of the obscurity surrounding the problem and our ignorance of it. The history of diseases shows that the moment there is certainty about a given disease, all the different terms like 'true', 'false', 'pseudo' disappear immediately.

How could this 'hopeless' situation have arisen, and why is it apparently impossible to bring clarity to these simple and uncomplicated conditions, anacidity, achlorhydria, achylia gastrica? Our first and most important question, therefore, is one of definition.

Today's definitions are:

Achlorhydria: Lack of hydrochloric acid

Anacidity: Lack of acid

Achylia gastrica: Lack of hydrochloric acid and ferments.

We are at a point where achylia gastrica must be rediscovered. It is always helpful and enlightening, if there is something obscure about a disease, to go back to the papers of those who first described it. In his excellent monograph, published in 1897, Martius writes: "Achylia gastrica exists only when, besides hydrochloric acid, there is lack of the ferments. Yes, strictly speaking—and this will prove to be very important—there must be proof that there is *no secretion at all*." What does this mean: That, for a diagnosis of achylia gastrica, there must be lack of *all secretions*—rennin, pepsin, lipase, mucin, the intrinsic factor, water and whatever may be found in the future. It is what the name, exquisitely coined by Einhorn expresses—a-chylos—the stomach does not produce gastric juice; it is free from any juice whatsoever, and therefore the emphasis should not be placed merely on lack of hydrochloric acid.

Does it not seem paradoxical to diagnose with a liquid test (alcohol) a condition the most important symptom of which is the absolute lack of gastric juice? Originally this entity was worked out by means of the Boas-Ewald test meal. When an easier method of testing for the intrinsic factor is found, the differentiation between achylia gastrica and achlorhydria will prove to be very simple.

The entity 'achylia gastrica' shows three strictly circumscribed signs:

1) Absolute lack of gastric juice, with lack of all the constituents of the gastric secretion.

No free HCl; chloride concentration very low; reaction is often alkaline. The quantity of liquid is minimal; only a few cc, presumably from the intake of tea during the test meal.

2) Disturbance of chymification.

There is no pulpy digestion of the gastric content, so the expressed residue of the test meal consists of what seems to be only chewed crumbs. There is little mucus; often traces of blood and particles of the mucous mucosa, due to the vulnerability of the mucosa.

A *liquid* anacid gastric content, even if it contains coarse bread particles, does not permit the diagnosis of achylia gastrica.

3) Disturbance of motility.

Increase of the expulsion phase of the stomach. The stomach expels the test meal generally in half the normal time up to a few scanty remnants. Normal expulsion time after Boas-Ewald's test meal is about 45 minutes; but in achylia gastrica it is accomplished in 20-25 minutes; the stomach is almost empty 40-45 minutes after intake of the test meal. One can observe the rapid emptying of the stomach on x-ray examination (it is just the contrary in achlorhydric conditions where we find a slow emptying time).

These three changes (in secretion, chymification, motility) are such typical findings after expulsion of the Boas-Ewald test meal that it is almost possible to make the diagnosis "achylia gastrica," as Martius once said, with the naked eye.

The alcohol test with histamine injection gives us information only on the hydrochloric acid secretion. Histamine refractory cases have been described where some time later free hydrochloric acid has been found; therefore the test no longer decides the differential diagnosis between achylia gastrica and achlorhydria (Henning, Henning and Norpoth, Faber). With these tests we cannot prove lack of secretion (although diminished secretion has been found by Goldhamer, Wintrobe; Bloomfield and Polland) and certainly not the chymification and motility of the stomach.

Only the Boas-Ewald test meal gives us proof of these three conditions and therefore must, of necessity, be used for a diagnosis of achylia gastrica.

II

All writers who consider achylia gastrica, achlorhydria and anacidity an identical condition because there is no free hydrochloric acid state that a *gastritis* with

inflammatory and atrophic changes is the cause of this condition.

In their opinion, the changes in the gastric mucous membrane are caused by a great number of external factors acting on the stomach, either by direct irritation of the mucous membrane or through the blood circulation by a toxic action on the gastric parenchyme (Faber).

The causes of this gastritis can be:

Gastric carcinoma, chronic gastritis, gallbladder disease, tuberculosis, Graves' disease, chronic arthritis, alcoholism, subacute combined sclerosis, pernicious anemia, hypochromic anemia, pellagra, sprue, anorexia nervosa, Simmond's disease, gastric lues, gastrogenous diarrhea, nephritis, diabetes mellitus, gastrogenous intestinal disturbances.

Mouth infections, focal infections, any infection (local and general), circulating toxins, allergic toxins. Acute infections: Typhoid, paratyphoid, pneumonia, influenza, dysentery, appendicitis, morbilli, diphtheria. Defective denture.

Irritants: Strong tea, coffee in excess; curry, pickles, pepper, mustard.

Drugs, such as: bromide, iodine, mercury, digitalis, quinine, salicylates; too many cigarettes.

Hot food, cold food, improper food, coarse food, decomposed food; too much food, too little food; rapid eating.

On the basis of this evidence, merely taken from textbook after textbook, one can only ask: Is there anyone who has no gastritis? Bloomfield and Polland rightly state that such a concept obviously reduces the whole subject to an absurdity! One might also ask: Is there such a thing as normal stomach mucosa? Guiss and Stewart have ascertained that 82 per cent of apparently normal persons who died within the cancer age (over 40) show, microscopically, evidence of chronic atrophic gastritis. Only at birth, and during the first and second decade did they find no pathological changes. In adults, the round-cell infiltration is actually to be considered *normal* (Benedict and Mallory; Paschkis and Orator; Hebbel, Hamperl, Hillenbrand, Jones, Magnus, Crohn).

The main advocate of the gastritis theory is Knud Faber. His idea is that primarily there is a gastritis which is produced by external factors, and this leads secondarily to the absence of free hydrochloric acid (Kuttner, Boas, Henning and others). Also, according to *Faber*, achylia gastrica or achlorhydria is always, and under all circumstances, a disease which develops in a stomach heretofore apparently absolutely normal, at any time of life, and as a result of external factors.

Martius has exactly the opposite point of view. He considers achylia gastrica a separate entity, having nothing in common with achlorhydria but the absence of free hydrochloric acid. He repudiates the exogenic factor for achylia gastrica. He sees in it a definite, permanent and unalterable condition without any gastritis. In his opinion, the glandular cells of the stomach develop histologically apparently normally, but they function poorly or not at all. It is this primary achylia gastrica simplex or constitutionalis—and it alone—this is closely connected with pernicious anemia.

In other words, there are two entirely different fundamental opinions: According to the prevailing opinion, achlorhydria or anacidity or achylia gastrica are the same disease—merely different names for the same condition. The opposite opinion differentiates between achylia gastrica and achlorhydria or anacidity: 1) *Achlorhydria* is lack of free hydrochloric acid; a symptom found in many conditions and of no clinical significance; secondary to exogenic causes. 2) *Achylia gastrica*, on the other hand, *is complete absence of gastric juice; primary, constitutional and the precursor of pernicious anemia.*

To prove the accuracy of the supposition that achylia gastrica differs from achlorhydria, it was of the greatest importance to know whether a gastritis is really always the cause of the disappearance of free hydrochloric acid, and whether the pathological changes are the same in achylia gastrica as in achlorhydria.

The first who contradicted Faber's opinion was Weinberg (1918), after the examination of eleven stomachs of patients with achylia gastrica who died of pernicious anemia. He stated that there was no gastritis at all in any of his eleven cases.

He divided his cases into three groups: Group 1. Three cases: No changes of gland cells; only very slight round-cell infiltration; no atrophy. Group 2. Five cases: Slight atrophy; slight gland cell changes in cardia and fundus; pylorus free. Group 3. Three cases: Intense atrophy of cardia and fundus; pylorus free.

The result of these examinations was:

1) The pathological changes were limited to fundus and cardia; pyloric region showed no changes, even in cases with intensive atrophy.

2) In three of eleven cases there was no change whatever of the gastric mucosa which was normal.

There were cases with only slight atrophy, others with progressive atrophy.

There was *no* inflammatory gastritis in the eleven cases of achylia gastrica in pernicious anemia. A gastritis, consequently, cannot have been the cause of lack of gastric juice. Achylia gastrica can exist with normal gastric mucosa.

Einhorn, Lubarsch have described the same phenomenon on the basis of examinations of mucosal particles; Ricker, in 1906, described the postmortem findings of the stomach mucous membrane of a patient with achylia gastrica, who died of pernicious anemia, as *"absolutely normal"* ("no gastritis, no atrophy"). Lubarsch and Borchardt showed that in 16.5 per cent of their 121 cases of pernicious anemia even roughly recognizable pathological changes of the stomach did not exist. Passey (1922) found normal oxyntic cells and no evidence of inflammation in a fragment of gastric mucous membrane removed during an appendectomy on a patient with Addison's pernicious anemia; Madeleine Brown found one case of pernicious anemia with entirely normal mucosa. Crohn, Hurst speak of simple achylia gastrica with normal gastric mucosa; Wallgren among 18 cases, in three cases "no atrophy could be traced out."

The findings of Weinberg—no inflammation and no pathological changes of the pylorus—are confirmed

by Magnus and Ungley (1938), Meulengracht (1939), Cox (1942), Wallgren (1943).

Magnus and Ungley examined seven cases in which they found severe atrophy but no evidence of past inflammation. In all seven stomachs there was atrophy of fundus and cardia, but no suggestion of atrophy or inflammatory lesions in the pyloric mucosa. They conclude that the gastric lesion present in pernicious anemia is not the end result of an inflammatory gastritis; it is regarded as an atrophic process, the cause of which is not known. Cox saw the same picture in six, Meulengracht in eight cases. Cox found the lesions in the cases of pernicious anemia different from those of so-called "chronic gastritis," to the extent that the changes and distribution may represent a "specific change."

Wallgren, on examination of 18 cases of pernicious anemia, found atrophic changes in the fundus. Contrary to the results of the other examiners, however, he saw pathological changes in the mucosa of the pylorus, too. But the atrophy was much more evident in the fundus than in the pylorus. While all authors found only high atrophy, Weinberg and Wallgren saw a gradual transition—from normal to intensive atrophy:

	No atrophy	*Mild atrophy*	*Intensive atrophy*
Weinberg	3	5	3
Wallgren	3	4	8

Bockus, Bank and Willard; Jones, Sturgis and Goldhamer; Doig and Wood confirm the findings that it is not a question of an inflammatory process. It is an atrophic degeneration of the secretory structure. In my opinion, it is a progressive *inactivity atrophy;* "disuse of structure results in atrophy" (McCallum). If we have inflammatory changes in cases of achylia gastrica, and no doubt there can be such, they are of secondary nature and have nothing to do with the presence of achylia gastrica.

An explanation for the peculiar findings, that only the cardia and fundus of the stomach show atrophic changes whereas the pylorus is free, has been given by Fox and Castle. They proved "that, in men, the important sites of secretion of the intrinsic factor are in areas containing the fundus type of glands and that the observations suggest that the source of the intrinsic factor in the normal human stomach coincides with the site of the degenerative process seen in histologic preparations of the stomach in pernicious anemia;" confirmed by Landboe-Christensen and Plum.

III

Although it has been known for a long time that free hydrochloric acid is absent from the stomach in cases of pernicious anemia, there have been attempts to prove otherwise. Wintrobe speaks of lack of free hydrochloric acid in at least 97.6 per cent of cases; he finds "at least 36 cases have been described in which free hydrochloric acid was found in the gastric secretion of otherwise typical cases of pernicious anemia." Naegeli estimates that achlorhydria is found in 98 per cent of all cases of pernicious anemia.

When I started my work on pernicious anemia, I was astonished to find that in *all* my cases (105 at that time) hydrochloric acid was absent; but the condition was not merely absence of free hydrochloric acid—it was typical achylia gastrica simplex or constitutionalis. Martius (1897) had already recognized the association of achylia gastrica—not achlorhydria—with pernicious anemia.

The question was: Is pernicious anemia regularly, and without exception, accompanied by achylia gastrica? With this in mind, a careful study was made of all cases of pernicious anemia described with *normal* gastric juice. Not a single case was found which was an actual case of pernicious anemia (1918).

Since that time, a number of cases of pernicious anemia with free hydrochloric acid again have been described. In his critical analysis of these cases, Askey reported on 47 cases with free hydrochloric acid, but "none of these 47 cases has been proved by complete precise criteria to be Addison's pernicious anemia" (1944). Again and again, certain cases are quoted which attempt to demonstrate the existence of Addison's pernicious anemia with free hydrochloric acid. Such are Castle's two cases. But Castle himself diagnosed one of these cases as sprue; the other as "macrocytic anemia with chronic diarrhea following operations resulting in multiple intestinal anastomoses." In addition, there are the two cases by Barnett, of which Bloomfield and Polland say "they are a stumbling-block to the categorical acceptance of the theory of achylia gastrica with pernicious anemia." In my opinion, both cases are sprue although Barnett calls one of them "atypical primary anemia."

Recently, two more cases have been published as Addison's pernicious anemia, with normal gastric acidity and no intrinsic factor. In A. Murphy's case, however, the sternal biopsies first undertaken after the beginning of liver treatment and for the second time during relapse—did not show the typical picture: "failure to disclose a megaloblastic marrow picture." All the "logical and adequate reasons to explain it" for the second sternal biopsy cannot be considered valid. In this case of Murphy's we do not find a typical example of the disease, and the picture is more normocytic than macrocytic. To draw such an important conclusion, i.e. that achlorhydria (he does not say achylia gastrica) is not essential to the development of Addison's pernicious anemia, one must describe an absolutely incontrovertible case. Here only facts and not explanations count.

Benjamin's case (infantile form of pernicious anemia), with normal gastric juice and no intrinsic factor, differs from the normal picture of pernicious anemia: There was no tendency to the development of spontaneous remissions, so characteristic of pernicious anemia—not only in adults, but also in typical cases of childhood. As a result, today, no doubt, all who write with authority are of the opinion that a diagnosis of Addison's pernicious anemia with normal gastric juice must be an error (Martius, Weinberg, Askey, Ewald, Zadek, Wintrobe; Bloomfield and Polland; Bockus, Bank and Willard; Wilkinson, Goldhamer, Sturgis, Crohn, Schwartz etc.). The fact is stressed that the disturbance of the gastric secretion (achylia gastrica) in pernicious anemia never changes, in spite of liver therapy and an absolutely normal blood picture; the achylia gastrica is unchangeable.

In the future it must be determined whether the gastric content in dubious cases shows a typical picture of achylia gastrica, or whether it is only achlorhydria. The work of Castle has given us a better understand-

ing of the connection between achylia gastrica and pernicious anemia. He proved that the gastric juice contains a substance—the intrinsic factor—which acts on an element present in protein food—the extrinsic factor—to produce the normal stimulant, the anti-anemic substance, for the formation of red blood corpuscles in the bone marrow. The result of the absence of the intrinsic factor is the blood defect characteristic in pernicious anemia.

No diagnosis of pernicious anemia should be permitted when there is no achylia gastrica; in the absence of achylia gastrica, pernicious anemia (Addison-Biermer) does not exist.

That achylia gastrica is something totally different from achlorhydia can be proved when we compare the achlorhydria in other conditions (such as cancer of the stomach, tuberculosis or alcoholism) with achylia gastrica in pernicious anemia.

Let us give some statistics. In tuberculosis of the lungs, Permin and Hansen saw in 658 cases: Achlorhydria (and hypochlorhydria) in 38 per cent, divided as follows:

Stage I: 23 per cent, Stage II: 34 per cent, Stage III: 47 per cent. In cases that died at least six months later: 75 per cent. We see, therefore, that the frequency of anacidity depends upon the stage of the disease. Torning saw only 6 per cent, Henning 26 percent anacidity.

The same picture is evident in cancer of the stomach. Hydrochloric acid diminishes during the course of the disease from normal to zero (Riegel).

	1) *Hartman*	2) *Mimes and Geschickter*
Among 551 cases of stomach cancer:		Among 339 cases
Anacidity	54 per cent	64.6 per cent
Hypoacidity	16 per cent	35.9 per cent
Normal values	17.5 per cent	6.7 per cent
Hyperacidity	4.5 per cent	——

Bloomfield and Polland saw loss of hydrochloric acid (with histamine test) in 69 per cent; Kelling, 75 per cent (622 cases); Hurst, 65 per cent (74 cases); Brunschwig, Schmitz and Rasmussen in about 60 per cent: Hebbel and Gaviser, 65 per cent. That the increase of achlorhydria is concurrent with the progress of cancer is shown in White's statistics:

Anacidity in group of earlier cancer: About 50%.

Anacidity in group of later cancer: About 75% up to 80 or 90%.

The presence of free hydrochloric acid is closely related to operability (White, Katsch, Eusterman and Bueerman).

Let us consider another condition very often associated with achlorhydia: Alcoholism. In 128 patients who were confirmed alcoholics, Vogelius found in 56 per cent of them achlorhydia on admission. In a large number of patients this achlorhydria disappeared quickly with treatment.

On the other hand, the development of achylia gastrica has never been observed (Weinberg, Cornell, Wilkinson and others). Not one case of pernicious anemia has been reported where normally functioning gastric mucosa was demonstrated before the start of the disease. Many cases have been documented in which achylia gastrica has been found up to 40 years before the manifestations of pernicious anemia (Einhorn, Schauman, Martius, Weinberg, Sturtevant, Queckenstedt; Cornell, Riley, Faber, Eggleston, Cobert and Morawitz; Johannsen, Askey, Strandell, Meulengracht, Vanderhof; Rozendaal and Washburn, Jorgensen and Warburg, Beebe and Wintrobe, Lichty and others).

CONCLUSION

Achlorhydria in cancer, tuberculosis and other diseases can be observed in its origin. There is a gradual, progressive diminution of free hydrochloric acid which parallels the progressive severity of the disease. Achlorhydria, therefore, is to be found only in a certain percentage of the cases. When the benign condition is cured—as in alcoholism and bad teeth—it is reversible.

Achylia gastrica, in sharp contrast, is to be found in pernicious anemia 100 per cent. It is never progressive. It is present not only at the onset of the disease but prior to it.

IV

There is no longer any doubt that achylia gastrica precedes the rise and development of pernicious anemia; but there is no agreement about the significance of this pre-existent achylia gastrica.

There are two opposing points of view: 1) Achylia gastrica is the earliest prodromal symptom of pernicious anemia, often present before the onset of pernicious anemia. (Both of coordinate origin, Faber; collateral phenomenon, Meulengracht.) 2) Achylia gastrica is the basis for the rise of pernicious anemia. Without achylia gastrica there is no pernicious anemia.

If observations were correct—that achylia gastrica always precedes pernicious anemia and that pernicious anemia cannot exist without achylia gastrica—then it should be possible to demonstrate the development of pernicious anemia, and to make an early diagnosis by systematic blood examinations of the cases of achylia gastrica.

It is evident that pernicious anemia must have a beginning and not, as formerly has been asserted, an *end* but *no beginning*. Of course there have been attempts to make an early diagnosis by the most exact observation of all signs and symptoms of pernicious anemia, but without any success (Plehn).

In my examination of 77 cases of achylia gastrica with 110 blood tests, I found four different types:

1) Cases with normal findings=22 per cent

2) Cases with hypochromic anemia (of chlorotic type)=26 per cent

3) Cases with hyperchromic ('normal') blood picture (latent cases)=17 per cent

4) Cases with pernicious anemia blood picture (early cases)=12 per cent

Of interest to us are groups 3 and 4 only.

These examinations showed that in a great number, the hemoglobin content was over 100 per cent and the amount of erythrocytes above 5,000,000.

In four cases we saw the findings of polycythemia (hemoglobin 130, 130, 135, 139; erythrocytes 6.1, 6.1, 6.4, 6.9 millions). Polycythemia has been found so often in connection with ulcus ventriculi that Bing be-

lieves it is due to the gastric secretion. On the other hand, there has been observed a transition from polycythemia to pernicious anemia (Freund; Minot and Buchman, Makarevicz, Avery; Delhougne, Gotschlich and Froboese, Christian). In Christian's case there was a longstanding achylia gastrica; Risak and Schur saw achylia gastrica in polycythemia.

The following is a case of achylia gastrica with very high hemoglobin and transition to pernicious anemia.

Female—56 years old

	Achylia gastrica	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*
1919		120	5,000,000	1.2	6,100
1920		110	4,000,000	1.4	6,400
1921		67	2,400,000	1.4	5,400

Patient died in 1924. Autopsy revealed pernicious anemia.

The leucocytes in our cases (108 examinations) were:

Normal (6,000-9,000) in 56 cases=52%
Increased (above 9,000) in 22 cases=20%
Diminished (below 6,000) in 30 cases=28%

The diminished amounts are distributed:

6—5,000 in 18 examinations
5—4,000 in 7 examinations
4—3,000 in 4 examinations
Below 3,000 (2,885) in 1 examination

The percentage of lymphocytes was increased (over 30 per cent) in 54 examinations (from 67 cases), equaling 82 per cent.

Let me give the picture of several blood examinations in personally observed cases of achylia gastrica.

TABLE I.

	Sex	*Age*	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*	*Lymphocytes %*	*Monocytes*
1.	M	31	92	4,300,000	1.1	11,000	43	3
2.	F	30	98	4,100,000	1.2	7,300	34	3
3.	F	45	106	5,000,000	1.1	7,800	30	2
4.	M	56	103	4,400,000	1.2	8,800	44	4
5.	F	47	90	4,000,000	1.1	4,700	34	0.75
6.	F	31	90	4,000,000	1.1	6,200	54	6.5
7.	M	46	105	4,900,000	1.1	6,200	40	3
8.	F	40	100	4,350,000	1.2	5,000	41	4
9.	M	56	86	3,800,000	1.1	5,700	43	1
10.	F	32	93	4,300,000	1.1	6,100	32	5.5

In case 1: Father died from pernicious anemia.
In case 2: Mother suffered from pernicious anemia.
In case 3: One brother has pernicious anemia.

The most striking feature in all these cases is the *macrocytosis*. With color index above 1 we see polychromacy sporadically, but very often poikilocytosis and anisocytosis. In all these cases there was relative lymphocytosis, often leucopenia with hypersegmentation; diminished monocytes, diminished platelets. In separate instances we saw normoblasts, in a few cases myelocytes and promyelocytes, even myeloblasts. The diagnosis in our cases was *latent* pernicious anemia. There are changes in the blood picture in microscopically small form, which, increased, would show the typical picture of pernicious anemia.

These ten cases were potential cases of pernicious anemia. In fact, seven of them developed pernicious anemia during the next six years. Three could not be followed.

Here are some of our cases (described by Stahl) with special consideration of the platelets.

TABLE II.

	Sex	*Achylia gastrica*	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*	*Platelets*
1.	F	+	110	4,000,000	1.4	4,900	365,800
2.	F	+	106	4,200,000	1.3	5,800	125,000
3.	F	+	100	4,700,000	1.1	5,100	90,000
4.	F	+	96	4,700,000	1.0	4,700	122,000
5.	F	+	94	4,100,000	1.2	5,100	126,000

The following case is an example of transition from normal to pernicious anemia observed for sixteen years. The patient was sent regularly by the state insurance company for examination at the hospital.

Male—32 years old in 1906

	Diagnosis	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*
1906	Achylia gastrica; neurasthenia	Tallquist 90-100	—	—	—
1908	Achylia gastrica	—	—	—	—
1909	Achylia gastrica	—	—	—	—
1915	Achylia gastrica	104	4,500,000	1.2	13,300
1918	Achylia gastrica	65	2,600,000	1.3	5,600
1921	Achylia gastrica	47	1,400,000	1.7	2,600
1922	Achylia gastrica	35	850,000	2.1	1,300

The patient died in 1922 (9 remissions). Autopsy showed pernicious anemia.

Achylia gastrica was only an incidental finding because in our hospital the gastric analysis was as routine an examination as urinalysis. In 1915, when I saw the patient for the first time, as in every case of achylia gastrica, the blood was examined. It was a so-called 'normal' specimen. Who would have thought of latent pernicious anemia with 104 per cent hemoglobin? Nevertheless, this diagnosis was entertained in view of past experience. Seven years later the patient died of pernicious anemia.

It was O. Schauman who first (1912) described a case that was at this time a very early case of pernicious anemia. Hemoglobin: 85 per cent; erythrocytes: 2,400,000; color index: 1.75; leucocytes: 3,700 with

30 per cent lymphocytes; poikilo-anisocytosis; strongly marked megalocytosis, and of course, achylia gastrica. The hemoglobin content was extremely high for a diagnosis of pernicious anemia at this time. It caused Schauman to establish the very important fact (not yet totally understood and valued) that there can be pernicious anemia with normal and above normal hemoglobin content. Naegeli's and Zadek's early cases show the same picture.

Naturally there exist examinations of the blood in achylia gastrica, but, strange to say, very few and of only two kinds: Normal cases and cases with hypochromic anemia. All writers have been interested only in studying the connection between achylia gastrica and hypochromic anemia. All the non-anemic cases are registered as 'normal'.

Among Einhorn's cases of achylia gastrica, two showed pernicious anemia; eleven were 'normal'. But two of his 'normal' cases are of particular interest:

	Age	*Hemoglobin*	*Erythrocytes*	*Color Index*	*Leucocytes*
1.	30	100	4,235,000	1.2	5,700
2.	23	100	4,580,000	1.1	7,600

Among Polland's 56 cases I find eight described as 'normal', with a color index above 1 (hemoglobin in 3 cases: 100, 105, 107). Meulengracht described a case of a child with achylia gastrica, a blood relative in a family with pernicious anemia. The examination showed: Hemoglobin, 98; red cells 3,000,000; color index 1.6; megalocytosis; average red cell diameter, 8.8μ; leukopenia, bilirubinaemia, urobilinuria; glossitis. Cary found in 4 out of 23 cases a high color index. Askey writes about 'normal' blood findings, but in six cases the color index is above 1, and in three there is macrocytosis. He considered 10 of his 61 cases with achylia gastrica "potential cases of pernicious anemia who in later years might develop the disease." Over a six year period, four in fact developed apparent incipient pernicious anemia (relatives of patients with pernicious anemia). Borgbjärg and Lottrup saw the color index over 1 in 22 among 134 patients; megalocytosis was found in 15 per cent, most often in patients with high color index.

In 18 of his white counts, Carey found the total average of leucocytes less than 7,000; in 3 cases, less than 5,000. Kohn saw a low number of leucocytes in 10 cases. In the last few years, further observations have been published of achylia gastrica with color index above 1, and megalocytosis (Frank; Ungley and Suzman; Chevallier, Lehmann—these French authors call it métanémie; Warburg and Jorgensen; Beebe and Wintrobe). Only Rozendaal and Washburn obtained different results: Among 36 cases with achlorhydria, they found the color index above 1 in only 2 cases; in all others, within the normal range.

The transition from achylia gastrica to pernicious anemia has been seen by Strandell who examined 117 cases of pernicious anemia. In 22, the gastric juice was searched several years before pernicious anemia appeared. Of course, there was no indication or even suspicion of pernicious anemia at that time. All 22 cases had achylia gastrica and a few years later pernicious anemia. Unfortunately, only two blood examinations were made in these 22 cases:

		Hemoglobin	*Erythrocytes*	*Color Index*	*Leucocytes*	*Achylia Gastrica*
Case 1.	1916	80-90	5,000,000	—	5,900	+
	1917	40	—	—	—	+
	1918	56	1,763,000	1.6	5,888	+
Case 2.	1922	95	5,000,000	.95	6,200	+
	1924	38	1,400,000	1.4	5,800	+

Diagnosis in both cases was pernicious anemia.

One case by Schauman:

	Hemoglobin	*Erythrocytes*	*Color Index*	*Leucocytes*	*Achylia Gastrica*
1911	93	3,660,000	1.2	3,660	+
12/19/1919	67	2,530,000	1.3	2,100	+
12/26/1919	52	2,240,000	1.3	2,000	+

Martius (1897) described among 17 patients with achylia gastrica two who under his observation developed pernicious anemia. There are other cases by Hutchinson, Meulengracht; Schneider and Cary (4 cases); Schemm, Frank (twins), Askey, Strandell; Kaufmann and Thiessen.

Bloomfield and Polland reject the connection between achylia gastrica and pernicious anemia, because they have observed 64 patients with total anacidity for varying periods up to five years without the development of pernicious anemia. Barnett, Crohn; Wilkinson and Brockbank are of the same opinion.

Wills points to the importance of the time factor: After total gastrectomy, there may be a period as long as ten to fifteen years between the time of operation and the development of symptoms. The time element is again indicated in Schemm's record: Mother and son had achylia gastrica; the mother developed pernicious anemia at the age of 63, the son at 24.

V

For a long time there was a controversy as to whether achylia gastrica occurs among infants and children. One believed it to be nonexistent so early in life.

In recent years, however, numerous cases have been described which prove beyond a doubt that achylia gastrica does occur among newborn infants and children. Among infants it has been described by Lehmann—1 out of 30, 12 months old, histamine-fast achylia gastrica; Faber and co-workers—6 out of 10, ages from 7 months to two years; Cutter—4 out of 10 healthy infants in the neonatal period with histamine; Miller—6 out of 50 normal infants examined

daily for the first ten days of life; Peterson and Dunn—girl, 13 months old; Zuelzer and Ogden—9 out of 10 infants, ages 2 to 16 months with histamine; Dedichen—girl, 9 months old.

Zuelzer and Ogden call our attention to the fact that achlorhydria in infants must be interpreted with a great deal of caution. In many cases it cannot be definitely decided, on the basis of the histamine test alone, whether it is a case of achylia gastrica or achlorhydria. Several cases, however, have been described where achylia gastrica still existed when reexamination was made after many years: Miller, 2 years later; Faber, first examination at 8 months, reexamination 7 years later; Peterson and Dunn, from 13th month, followed to the age of 5½ years.

As long ago as 1913, Albu described achylia gastrica among children: 34 cases of achylia in children under 10 years; his youngest was four years old. He observed family occurrence seven times. Martius, Queckenstedt, Weinberg have long ago shown the occurrence of achylia gastrica among children of parents with pernicious anemia; later, Wilkinson and Brockbank, Siemsen; McLachlan and Kline; Moschcowitz and Crohn, Martinez and others. Copeman and Hill reported 7 cases in 66 normal children between the ages of 12-15; Wright saw only 1.6 per cent in children from 6-15 years. (Others by Katsch, Schmidt.)

Achylia gastrica is accompanied in children by the same changes of the blood as in adults: Hypo- and hyperchromic anemias. From a remark of Leonard Findley, however, we learn that he has come across children in whom he found an "idiopathic achlorhydria" with *no obvious anemia.*

In hypochromic anemia the achylia gastrica persisted after the anemia had been cured by the administration of iron (Hawksley, Lightwood and Bailey, Wilson; Dacie and Elman, Ogilvie and others). In cases of hyperchromic or macrocytic anemia, we must distinguish between two separate types. There are those with macrocytic blood picture, normal gastric secretion or temporary achlorhydria; complete and permanent recovery can be brought about by diet or liver or folic acid (Zuelzer) treatment, spontaneous recovery; no tendency to relapse (Zuelzer and Ogden, Veeneklaas). The others have achylia gastrica, marked tendency to relapse and need continuous treatment. Only these cases should be considered pernicious anemia Addison-Biermer. Peterson and Dunn want "the use of the term 'pernicious anemia in childhood' to be restricted, as it is in general medicine, to those cases of macrocytic anemia in which there is a complete and continuous achlorhydria, in which the patient shows a specific response to liver therapy, and in which continuous therapy is required to maintain the patient in a state of remission." In order to obtain absolute clarity, we shall, in future, speak of achylia gastrica instead of 'complete and continuous achlorhydria.' Parson and Hawksley, Davis; Karlström and Nordenson share this view on achylia gastrica.

If we consider these rigid and justified demands as a basis, we can regard only a few cases as typical pernicious anemia. Peterson and Dunn: Girl, with anemia from 8th month, followed from the age of 13 months to 5½ years; Dedichen: Boy, followed from the age of 9 months to the age of 3 years; Edgren and Segerdahl: Boy, aged 1½ years, under observation to the age of 3 years; Langmead and Doniach: Boy, 13 months, follow-up period 3 months; Pohl: Girl, 13 years old, follow-up period 3 years; Kade: Boy, followed from 7 to 14 years of age; Murphy: 11 years old, observed 3 years; Jacobsen: Boy, 14 years old.

We have four cases of pernicious anemia occurring in infancy which satisfy the strictest critic. Among older children, more cases are to be definitely regarded as pernicious anemia, even though they do not meet the requirements of Peterson and Dunn, since they had been described prior to liver therapy (Kusunoki, von Seht, Hotz, Brückner).

Stewart is of the opinion that achylia gastrica is not found in healthy children. Miller emphasizes that his infant with achylia gastrica was a "strong healthy child" from birth. Cutter mentions expressly that his children were healthy ones. It is to be assumed that Stewart confuses achlorhydria with achylia gastrica. There is no "cause" of achylia gastrica; it is inborn, as Miller's case proves.

To penetrate deeper into this question, we must make systematic stomach examinations of the children of parents suffering from pernicious anemia or achylia gastrica.

VI

An important element in achylia gastrica is *heredity.* P. White and G. Pincus have stated four factors in favor of the theory that the potentiality for developing diabetes is inherited. In a separate paper, I have shown the likeness of the conditions in diabetes and achylia gastrica. The four factors prove the same for achylia gastrica.

First Factor: Almost simultaneous occurrence of achylia gastrica and pernicious anemia in both members of identical twins.

Second factor: The greater incidence of achylia gastrica and pernicious anemia in the blood relatives of patients with achylia gastrica and pernicious anemia than in those of a control.

Third factor: The demonstration of Mendelian ratio.

Fourth factor: The demonstration of expected ratios for achylia gastrica and pernicious anemia in presumably latent cases.

The *first factor:* The occurrence of achylia gastrica and subsequently of pernicious anemia in uni-ovular twins proves the influence of heredity. We have knowledge of seven definite cases of identical twins with achylia gastrica (Strandell, Ellis, Frank, Werner; Kaufmann and Thiessen, Bremer, Stamos). Four pairs had achylia gastrica with pernicious anemia; in the three other pairs, one twin had pernicious anemia and the other achylia gastrica developing into pernicious anemia.

Frank's case is a good example of the development from achylia gastrica to achylia gastrica with macrocytosis to pernicious anemia:

Twin brothers—aged 57. One has achylia gastrica with pernicious anemia. Other twin has achylia gastrica. *Blood is normal.*

Ten months later: Second twin, hemoglobin normal; color index 1.13. Achylia gastrica with *macrocytosis.*

Fifteen months later: Both brothers have *pernicious anemia.*

The *second factor:* The familial occurrence of pernicious anemia is a fact. In the course of recent years, many single cases and family observations have been published in which the appearance of the disease in several members of one family has been shown. Complete statistical studies have been given by Wilkinson and Brockbank, and by Stamos. Further evidence is shown by MacLachlan and Kline in four generations; Mustelin, Schwartz in three generations; five members in one family by Bramwell, Wilson, Askey, Patek, Dorst, Schemm, Moschcowitz and many more.

What of the familial occurrence of *achylia gastrica?* Biedert, as early as 1895, pointed out the possibility that the lack of gastric secretion is a familial attribute, inborn by predisposition or hereditary in its origin.

Weinberg, led by the fact of the invariable occurrence of achylia gastrica in pernicious anemia, for the first time systematically examined relatives of patients with pernicious anemia for achylia gastrica and found it in 29 per cent. Conner saw familial achylia gastrica in 25.9 per cent, Askey in 16 per cent, Wilkinson and Brockbank in 24.1 per cent.

Askey, Werner, Kaufmann and Thiessen saw achylia gastrica in relatives of pernicious anemia patients to be twice as high in *near* relatives as in *distant* ones.

	Near Relatives	*Distant Relatives*
Werner	19 per cent	9 per cent
Kaufmann and Thiessen	17.1 per cent	9.4 per cent

Among the general population, the number of achylia gastrica was 13.7 per cent by Hartfall; Andreasen, Eggleston saw it in 10 per cent, Jeffrey in 11.8 per cent, Conner in 15.2 per cent. In contrast, Bennett and Ryle found it only in 4 per cent among 100 healthy medical students; Lander and MaClagan in 1 per cent; Doig and co-workers in only 1 out of 134 students.

The comparison of the findings shows:

1) Occurrence of pernicious anemia in relatives of patients with pernicious anemia.

	Per Cent
Schemm	18.70
Castle and Minot	18.00
Schwartz	18.00
Kaufmann and Thiessen	16.70
Werner (about)	9.00
Schneider and Carey (between 6 and 12%)	9.00
Wilkinson and Brockbank	8.75
Naegeli (about)	8.00
Stamos	7.90
Levine and Ladd	6.30
Average	12%

2) Occurrence of achylia gastrica in relatives of patients with pernicious anemia.

	Per Cent
Weinberg	29
Conner	25.9
Wilkinson and Brockbank	24.1
Zadek	21.7
Askey	16.4
Schneider and Carey (at least)	12
Kaufman and Thiessen (near and distant relatives)	13.25
Werner (near and distant relatives)	14
Average about	19.6%

Of the *third factor* we can only say that a definite conclusion regarding the mode of hereditary transmission cannot yet be stated. We lack real demonstrable scientific hereditary research. Mustelin, Weitz; Kaufmann and Thiessen, Werner are of the opinion that achylia gastrica is transmitted as a dominant characteristic.

Fourth factor: Demonstration of expected ratios in presumably latent cases. The blood examination of my 77 cases of achylia gastrica showed 29 per cent had changes which allowed the diagnosis of latent or early pernicious anemia. In a great number of such cases it is possible to observe the transition to pernicious anemia.

Another factor, to which Colwell called attention in diabetes mellitus, is the so-called "anticipation." This means that a hereditary disease in three generations of a single family appears from generation to generation at an earlier age. In Mustelin's case, pernicious anemia appeared in the mother at 67, daughter at 42, grandchild at 24; all had typical achylia gastrica. We assume that, due to the congenital achylia gastrica, there is a diminished storage of the antianemic principle in the liver, and that the exhaustion becomes effective at an earlier age in each successive generation.

Additional interesting evidence for heredity has been given by Horsters and Krohn: In one family in which mother and oldest son had pernicious anemia, there was at the same time an inheritance bound to blood group A. Besides these two manifest cases, all members of the family with blood group A had a hyperchromic blood picture.

Further proof of heredity is given by the pathological findings. We have seen cases of achylia gastrica who died of pernicious anemia without atrophy of the gastric mucosa; the gastric mucosa was normal (Weinberg, Wallgren).

In their comprehensive statistics, Wilkinson and Brockbank differentiate among three groups:

1) Families with two or more members affected with pernicious anemia.

2) Families in which pernicious anemia and achylia gastrica existed simultaneously.

3) Families in which achylia gastrica was found without pernicious anemia.

In reality there is only *one* group: The families with achylia gastrica. Some of these achylic members will develop pernicious anemia. Wherever there is a family tree with achylia gastrica, there is a mixed occurrence of achylia gastrica and pernicious anemia. I, personally, have never seen families where the members had nothing but pernicious anemia or achylia gastrica (groups 1 and 3); careful and extensive examination always showed that achylia gastrica and pernicious anemia existed simultaneously.

VII

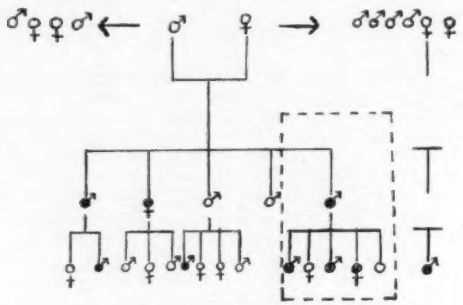
What is the practical value of true hereditary incidence in achylia gastrica?

We have seen that it is possible to make the diagnosis of pernicious anemia in its latent stage with normal or above normal hemoglobin and erythrocytes. We are familiar with the deficient factor in the form of liver or other substances; we know persons with achylia gastrica are potential cases of pernicious anemia: Is it not then logical to give such persons the lacking substance as soon as possible, thereby

forestalling the development of pernicious anemia and subacute combined degeneration of the cord?

The task is to find these cases with achylia gastrica constitutionalis. The procedure is systematically to examine all the relatives of a patient suffering from pernicious anemia or of a patient with achylia gastrica constitutionalis. Otherwise, it is a chance finding because people with achylia gastrica do not 'suffer'; they rarely have complaints. They do not visit a physician's office, especially not the gastro-enterologist's. To get valuable results, there must be an examination of every patient's genealogical tree—of all the living antecedents and descendants. It must cover all collateral relatives, including aunts, uncles, cousins, etc. It has to be a clan-examination, so-called 'Sippschaftstafel,' which means all blood-relatives near and distant, first described by Crzellitzer.

Figure 1.



Genetic Diagram

Open circles: No gastric change
Filled circles: Macrocytic achylic anemia
Crossed circles: Achylia gastrica
Clan-examination: 21 relatives, indicating the familial incidence of achylia gastrica with macrocytic achylic anemia

Let us examine an actual case: In a patient with pernicious anemia, five children could be examined. Three had achylia gastrica. The family examination showed that, of the 21 relatives, 8 had achylia gastrica, and 4 out of those 8 had pernicious anemia. This examination did not reveal the source of the inherent factor. A thorough examination of sisters and brothers of the parents (four from his father's, six from his mother's side) gave no clue—the gastric examinations were normal. But an aunt (his mother's sister) had married a man whose name was on our list of patients with pernicious anemia, and a grandson of hers actually had pernicious anemia.

For the detection of other cases of achylia gastrica or pernicious anemia, all the descendants of the six uncles and aunts of our patient should have been examined. This is the only way to find the persons with achylia gastrica. It is a formidable task. But it must be done and it has already started in Germany and Italy.

The method of procedure should be as follows: A certain institution in a given district is appointed, to which every case of pernicious anemia should be reported, by the physician or by the hospital: Name, address, diagnosis. From here the work starts: The institution must search the whole genealogical tree of the patient with all the collaterals. (A similar but more comprehensive method was followed in diabetes mellitus which proved very successful, Wilkerson and Krall). A gastric analysis and blood examination have to be performed upon each of these relatives. Those with achylia gastrica are potential cases of pernicious anemia as long as they live (see case of Schemm, page 357).

What should we do with these persons with achylia gastrica constitutionalis who seem to be absolutely healthy and have 'normal blood?' There are two possibilities. The first is the scientific way: To examine these persons at regular intervals, for instance every six months, to find out how many of them show blood and nerve changes in the course of time, and the rate of development. The second way is to treat these potential cases prophylactically, with liver or the other helpful substances, so as to prevent the development of pernicious anemia.

I am convinced that in all the cases of achylia gastrica constitutionalis, in which we have seen the transition to pernicious anemia, well-timed treatment with the antianemic principle would have averted the manifestation of the deficiency disease (see the cases of Strandell, Askey, Frank's twin brother, Meulengracht, Dorst, our own cases).

It is a 'mass experiment' and will achieve its goal only after a long period of time. But the goal will be worth while: The prevention or eradication of pernicious anemia. To achieve this goal we must enlighten physicians and patients alike. The physician must have more knowledge about the heredity of achylia gastrica and its connection with pernicious anemia, and he must convince the patient with pernicious anemia of the necessity for family examinations. It was never a difficult matter to explain this to our patients; most patients are interested in the facts of heredity and are grateful for enlightenment. While there were never any difficulties in obtaining consent for the blood examinations, there were sometimes objections to the gastric examinations; but these objections must somehow be overridden since, of the two, gastric examination is the more important.

The blood examination should not be just routine; it should be effected with special care and with appreciation of all useful methods (platelets, erythrocyte diameter, bone marrow puncture).

Originally the disease was named progressive pernicious anemia. To distinguish it from the other macrocytic anemias, it is at present known as pernicious anemia Addison-Biermer. It is time to give the disease a more accurate name, since the word 'pernicious' fortunately no longer applies; the disease is one of deficiency marked by an inborn, constitutional lack of gastric juice—achylia gastrica. Therefore the most significant designation for this disease is *'macrocytic achylic anemia.*

SUMMARY AND CONCLUSIONS

Achylia gastrica and achlorhydria are not synonymous.

Achlorhydria is lack of free hydrochloric acid, a symptom found secondarily in many diseases and conditions, and of no clinical significance.

Achylia gastrica is complete absence of gastric juice, primary and constitutional.

The differentiation is of greatest importance because achylia gastrica—not achlorhydria—leads to pernicious anemia.

The entity achylia gastrica shows three strictly circumscribed signs:

1) Absolute lack of gastric juice

2) Disturbance of chymification

3) Disturbance of motility

These three signs, necessary for the diagnosis of achylia gastrica, can be determined only by the Boas-Ewald test meal.

For the diagnosis of achylia gastrica the alcohol test meal with histamine injection is of minimal value, because it shows only the presence or absence of hydrochloric acid.

Achylia gastrica is not based upon a gastritis atrophicans. It can exist with normal gastrica mucosa. The changes are not inflammatory; they are atrophic—not in the pylorus, only in cardia and fundus—leading to the final stage of inactivity atrophy.

Blood examinations in achylia gastrica often show hemoglobin and erythrocyte values above normal. In many cases so-called 'normal blood' has been found, but there were changes which permitted the diagnosis 'latent or early penicious anemia.' There is macrocytosis with Color Index above 1, lymphocytosis, leukopenia with hypersegmentation, diminished monocytes, diminished platelets. From this stage the development of pernicious anemia has been seen.

The achylia gastrica is unchangeable. The development of achylia gastrica has never been observed.

Achylia gastrica has been detected in infants and children, especially in families where one parent had pernicious anemia. There is a familial occurrence of achylia gastrica; it is inborn, hereditary.

Our goal is to find these cases of achylia gastrica. For this reason all the relatives, antecedents and near and distant descendants, must be examined; a so-called clan-examination. It is suggested that these examinations be made at the central institution of a given district which collects all the names of patients with pernicious anemia and directs the examinations.

As potential cases of pernicious anemia, all persons with achylia gastrica must be under steady observation.

The question is: Shall we not give these people with achylia gastrica the factor necessary to forestall the development of pernicious anemia, and thereby, perhaps, eradicate the disease?

The name "pernicious anemia" is now misleading, since the disease is no longer pernicious. Furthermore, we have shown the importance of achylia gastrica which alone leads to "pernicious anemia." Therefore, because this disease belongs in the group of macrocytic anemias, I suggest that it be henceforth designated *macrocytic achylic anemia.*

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EFFECT OF A LYSOZYME INACTIVATING ANION EXCHANGE POLYMER IN TREATMENT OF PEPTIC ULCER: EXPERIMENTAL AND CLINICAL STUDY

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REGARDLESS OF THE various psychic factors that are invoked in the pathogenesis of chronic peptic ulcer, it is generally agreed that the combined action of hydrochloric acid and pepsin are determinant factors both in its persistence, the failure of healing, and the production of symptoms. In 1910 Schwartz (1) enunciated the dictum "No acid—no ulcer," a statement confirmed as recently as 1949 by the work of Palmer and his school (2). As stated by them, "Chronic peptic ulcer occurs only in association with acid gastric secretion; achlorhydria lasting longer than 3 months produces complete healing of peptic ulcer, irrespective of the age of the patient or the duration of the disease; and spontaneous or induced achlorhydria, if present, produces permanent healing of peptic ulcer." (2b).

Standard in all regimens of treatment of peptic ulcer has been the use of bland diets and antacids. Of the latter, a plethora of preparations is available. While some have produced satisfactory results, none are free of unpleasant side effects, and some, chiefly sodium bicarbonate, have actually shown serious toxic effects over prolonged periods such as ingestion alkalosis (3), and increased blood urea nitrogen (4). Thus, also, protein hydrolysates as recommended for ulcer therapy (5) have induced progressive rises in gastric acidity and prolongation of gastric emptying time (6). Even multiple cream and Sippy powder feedings have been shown to evoke an increased volume of gastric secretion, with increased acid and pepsin activity as compared with a single feeding (7).

The untoward effects have led to further search for potent antacids without these undesirable side effects. Adams and Holmes (8) first called attention to the adsorptive properties of synthetic resins in 1935, and these were first employed by Segal and associates (9) ten years later to reduce gastric acidity in rats. They, however, found such large amounts necessary as to make the clinical use of resins for this purpose of doubtful value. The difficulty was overcome by Martin and Wilkinson (10) who, by reducing the size of

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the resin particle from 40 mesh to 200 mesh, so increased the adsorptive capacity as to bring the amounts needed within the range of practicability. Subsequent clinical studies by Spears and Pfeiffer (11), Kraemer and Lehman (12), Weiss (13), Kasdon (14), Weiss, Espinal and Weiss (15), and Marks (16) have all shown anion exchange resins to be an effective antacid, of greater neutralizing power than those previously available per unit time and without unwanted side effects. While diets more liberal than those used in orthodox practice were employed in these investigations, it appears that some dietary restriction from the pre-therapy norm of the patient was invoked both as to the type and amount of food taken, and the feeding schedule. A very recent study of Wirts and Rehfuss (17) has confirmed the pepsin inactivating power of anion exchange polymer (Amberlite I R-4), and reduction in pepsin levels previously pointed out by Martin & Wilkinson (10) and the absence of acid rebound.

Recently Meyer and associates (18) have shown a significant increase in lysozyme in the gastric juice of patients with peptic ulcer, and Grossman (19) has produced gastro-duodenal ulcers in dogs by intragastric administration of lysozyme. In the course of studies on anion exchange polymers in our wards and laboratories, we noted one, Deacidite, that, in addition to its decidifying and apparent anti-pepsin effects, inactivated lysozyme. This resin we have employed in the treatment of 30 cases of gastro-duodenal ulcer. The study is the subject of this communication.

Deacidite is a formaldehyde aliphatic amine ion exchange polymer which is used industrially in water treatment plants. It has a high capacity for combining with HCl and does not lose the bound HCl easily. During the passage of the polymer down the gastrointestinal tract, the HCl eventually is split off and a series of equilibria is reached between the polymer and the intestinal juices. During our studies with this material as an antacid, we never were able to show a variation from normal of the blood serum Cl or plasma CO2 combining power. This is in contradistinction to the commonly used antacids which produce an alkalosis whose extreme effects, as a result of long-standing ingestion of alkalies, were recently described by Albright and associates (20). They showed that a syndrome of possible primary hyperparathyroidism with secondary renal damage could eventuate from the use of copious quantities of milk and absorbable alkalies, a routine common in the treatment of peptic ulcer. Hypercalcemia without hypercalcuria, azotemia, renal insufficiency, normal alkaline phosphatase and mild alkalosis were present in their cases, all giving a history or symptoms of peptic ulcer, and all having been on prolonged milk alkali regimen.

In our studies on pepsin inactivation, we came to the realization that the simple removal of HCl during pepsin hydrolysis prevents further enzyme activity. However, adding HCl to a point beyond the capacity of the polymer to react with the HCl, restored pepsin activity. (See Fig. II.)

In contrast, the activity of lysozyme is reduced sharply, by a process of denaturation or enzyme inactivation, providing the pH of the solution remains above 6.6. This, therefore, is not a reaction due to variations in acidity, but a direct effect of the polyamine on the hydrolytic enzyme.

METHODS

In all our cases, no attempt at dietary restriction was made save for the elimination of spicy, fatty, greasy or fried foods; and, since these cases were all ambulant, it is probable, as was very quickly realized from the remarks of patients' family who accompanied them on follow-up visits to the clinic or office, that even these restrictions were often not rigidly adhered to once the acutely painful phase was ameliorated. In the successful cases this generally meant that the dietary regimen, in whatever degree, played no material part beyond the third to seventh day after instituting the resin therapy. Similarly, though tobacco and alcohol were interdicted, it is doubtful, from collateral reports, that these dicta were well obeyed during the period of observation.

Approximately 20 Grams of Deacidite** were used per day. This was taken in 3 gram doses one to two hours following meals, 3 to 5 grams midway between the evening meal and bedtime, and, where night pains were severe or prominent symptoms, 5 grams were taken just before retiring. In cases 21 to 30 inclusive, the above routine was altered for the first two weeks of therapy to include two grams taken one-half hour before and 2 grams one hour after meals. No attempt at psychotherapy in any form was made in any case while under this regimen. In five cases (nos. 23, 25, 26, 27, 30), polymer that had lost its de-acidifying and lysozyme-inactivating power in vitro was submitted for the active polymer for a period of a week two weeks after all symptoms had disappeared. This inactive polymer, in its appearance indistinguishable from the active polymer, was substituted without the knowledge of the patient. In each instance symptoms of ulcer-activity—particularly night pain—recurred within two to three days of the substitution; all the patients wondered whether "the powder was the same," and all symptoms promptly subsided within a few days of resupplying the active polymer. Throughout the experiment the polymer was furnished the patients in cachet form. No sedatives or antispasmodics were employed during the experiment.

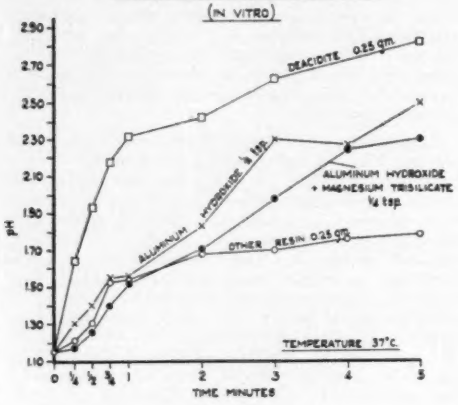
In this series of 30 consecutive, unselected cases, 24 were males, 6 females. The average age of the entire group was 35 years, with the range from the youngest at 28 years, to the oldest at 54 years. All but four of the patients had had symptoms of ulcer for over a year; 2 for 1½ years, 3 for 2 years, 2 for 2½ years, 6 for 3 years, 1 each for 3½, 4, 5½, 8, 9, 14 years, 3 for 6 years and 2 for 7 years. One patient had had symptoms for 2 weeks, 1 each for 2, 3 and 8 months. In one case the date of onset of symptoms could not be determined. In 27 cases the diagnosis of peptic ulcer was confirmed radiologically. One case (no. 28) revealed a duodenal diverticulum in addition to radiologic evidence of irritability of the cap. This case had been most refractory to Sippy therapy and, prior to coming under our care, had responded only to three weeks of continuous intrajejunal drip therapy, which clinical response had disappeared, and hunger and night pain had recurred within one month after such therapy had

**The Deacidite used in this study was kindly supplied by M. E. Gilwood of the Permutit Company, New York, N. Y.

been discontinued. Radiologic evidence of retention was noted in 10 cases (nos. 2, 3, 4, 5, 8, 11, 16, 17, 22, 27); in cases 5, 8, 16, and 27 it was 20% or more of the ingested meal on the 6 hour film. Night pain, to greater or lesser degree, was present in all cases in this series; in 12 cases (nos. 2, 3, 15, 17, 21, 23, 24, 25, 26, 27, 28, 30) night pain was severe and the presenting symptom.

FIG. 1

COMPARATIVE RATES OF REACTION OF ANTACIDS ON GASTRIC JUICE (IN VITRO)



RESULTS

The relevant clinical, laboratory and follow-up findings are summarized in table I. Here it is pertinent to survey, in broader outine, the results of the regimen.

1. Night pain disappeared completely in all except 4 patients (nos. 8, 11, 12, 16) within 48 hours after Deacidite therapy was instituted. In cases 5, 13, 23 and 25 an additional 5 gram dose was needed for from 3 to 6 days at the onset of the therapy to control night pain, after which period the single pre-bedtime dose sufficed.

2. Just as rapidly and completely as the night pain disappeared, so did the pain during the day in all but 2 patients (nos. 11 and 12). Even in these the pain was reported as lessened. Case no. 16, whose symptoms were predominantly due to obstruction, for which operative intervention had to be invoked during the experiment, showed no relief of symptoms. In the 27 patients experiencing disappearance of pain, the cessation of this symptom encompassed all forms of pain or distress, whether of the hunger type or of the fulness or gaseous discomfort variety.

3. Nine patients (nos. 22 to 30 inclusive) exhibited circumscribed epigastric tenderness at the initial examination. This tenderness totally disappeared in from 6 days to 3 weeks after polymer therapy had been instituted. One case of penetrating prepyloric ulcer (no. 21) exhibited such a degree of deep tenderness and muscle spasm that a diagnosis of impending perforation was suggested and surgery had been advised. This

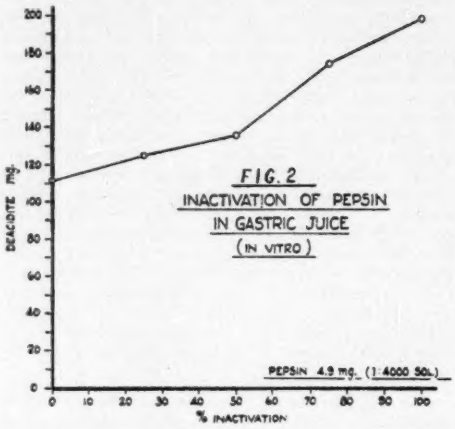


FIG. 2

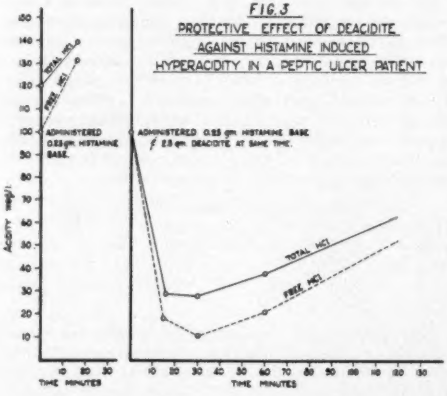
INACTIVATION OF PEPSIN IN GASTRIC JUICE (IN VITRO)

case, cited in detail below, showed one of the most dramatic symptomatic responses to the polymer, and, within 5 days of the disappearance of the pain, all evidence of tenderness and spasm had vanished.

4. As was to have been expected, the psychosomatic symptoms so prominent in peptic ulcer patients—mental irritability, lack of concentration, easy fatigability, weakness on a nonorganic basis—became less prominent or totally disappeared as the pain phenomena were relieved. This is again best illustrated in the case history cited below in which a veritable change in personality ensued. It was further noted in several cases that, without apparent change in business or social environment, these now pain-free patients seemed able to meet their usual daily stresses with total equanimity or with lessened reaction than before the regimen had been instituted. As noted above, no form of psychotherapy was employed during this period. The exceptions to this response again were cases 11 and 12, both with marked neurotic factors not previously nor subsequently aided materially by prolonged

FIG. 3

PROTECTIVE EFFECT OF DEACIDITE AGAINST HISTAMINE INDUCED HYPERACIDITY IN A PEPTIC ULCER PATIENT



psychotherapy. Even case 13, a borderline institutional patient, seemed mentally improved during the six month period of observation following polymer therapy, during which time he was free from pain.

5. Radiographic evidence of healing was evident in 22 patients within 2 to 6 weeks after instituting polymer therapy, and these changes were progressive toward restitution of normal outlines or scarring when re-surveyed months or a year or more after therapy had been discontinued. Of these cases, 4 (nos. 3, 28, 29, 30) showed complete restitution of the normal pattern, 13 (nos. 1, 2, 7, 9, 10, 17, 18, 20, 21, 22, 23, 24, 27) showed scarring. In nine cases (nos. 4, 7, 9, 10, 15, 17, 21, 27, 29) the niche or crater seen before therapy was instituted, either totally disappeared or was so diminished as to be perceptible only by close study after review of the earlier films. In case 25 the niche was one-quarter its original size 8 months after therapy was begun. In 5 cases (nos. 2, 3, 4, 5, 22) retention originally present was not found in films taken some months after therapy was instituted. Six patients (nos. 6, 11, 12, 13, 14, 26) showed no changes in the radiographic picture. Is is noteworthy, however, that of these, 3 (nos., 13, 14, 26) remained completely symptom free. In 2 cases (nos., 16, 19) no follow-up radiographic studies were performed. In no case was there apparent radiographic evidence of progressive worsening.

6. The effects upon gastric acidity, both free and total, are shown in the table. In each instance the test was performed in the fasting state. In cases 21, 23, 25, 26, 27, 28, 29 and 30, the second gastric analysis was performed six months after all therapy had been discontinued. The results in every instance demonstrated a decided diminution in both free and total gastric acidity while under the polymer regimen and this reduction to the normal levels appeared to be maintained in the 8 cases re-examined half a year after cessation of therapy.

7. Two cases (nos. 13, 25), symptomatically well controlled by polymer therapy, subsequently required surgery for recurrent massive intragastric hemorrhage. One of these (no. 13) had shown no radiologic changes following therapy: the other (25) had shown radiologic diminution of the crater to one quarter its pretherapy size. It should be noted that in the latter case, treated by excision of the ulcer, an extreme degree of fibrosis of the ulcer and a pronounced arteriosclerosis of the vessels was found on pathological examination. This patient, 48 years of age, was one of the older of the series.

8. One patient (no. 16) required surgery for the relief of obstruction. Polymer therapy in this case was carried on for only 5 weeks, during which time evidence of bleeding, in the form of tarry stools, developed.

9. No complications or sequelae of any kind attributable to the polymer was noted in any case in this series, either while under treatment or at any time thereafter. It was particularly noteworthy that constipation, so frequently a troublesome feature of the usual restricted dietary-antacid regimen and one often requiring active countermeasures, was never encountered in the patients on the unrestricted dietary-polymer regimen in this series. When it is recalled that continued use of mineral oil even in apparently healthy individuals with intact gag reflex may lead to lipoid pneumonia (21), the elimination of the need for this medicament through the use of the polymer is in itself a decided gain.

10. Of greatest value from the patient's standpoint, second only to the elimination of the pain, was the ability to utilize, from the beginning of the therapeutic regimen, the normal 3 meal schedule, without the necessity of intermediate feedings or of dietary restrictions often difficult to obtain in active daily working conditions. The psychologic effects of such normal living hardly need comment.

CONCLUSIONS

It can, therefore, be stated that in our 30 cases of peptic ulcer, the ion-exchange polymer Deacidite was found highly effective in 26 patients in eliminating all night pain within 48 hours of beginning of therapy, and in 27 patients in eliminating hunger pain. These effects were obtained without resorting to dietary restriction save for the elimination of seasoned food and alcohol, restrictions often not adhered to without untoward results. These symptomatic improvements were paralleled by the disappearance of circumscribed epigastric tenderness and muscle spasm, by radiographic evidence of healing, and by pronounced diminution of free and total gastric acidity. The polymer regimen did not prevent recurrent gastric hemorrhage in two cases, nor did it relieve a well marked gastric obstruction in one case, though in five cases the pre-therapy gastric retention noted radiographically disappeared under polymer therapy. No complications such as constipation or disturbances in acid or base balance occurred though the polymer was taken over a period of approximately one year.

In vitro experiments demonstrated that the anion-exchange polymer Deacidite used in these clinical studies, is a powerful and rapid deacidifying agent, with a minimal acid rebound effect. It is also shown that this polymer inactivates lysozyme. Its apparent pepsin inactivating effect is based upon its ability to remove hydrochloric acid, and is reversible. This is also partially true of its effect on lysozyme.

It is suggested that the anion-exchange polymer Deacidite is a highly satisfactory medicament in the treatment of peptic ulcer, and that its use permits of a dietary with minimal restriction as to content of meals and no disturbance of meal schedules from the usual adult average pattern.

Case No.	Patient	Age	Sex	Duration of Symptoms pre-medication	X-Ray findings before present treatment	Gastric Acidity before present treatment		Duration of present therapy	Gastric Acidity after pres. regimen		X-Ray Findings after pres. regimen	Remarks
						Free	Total		Free	Total		
1.	F. S.	37	M.	7 years	Duod. spasm "prob. ulcer"	84	92	6 weeks	x	x	Scarring of duod. 4 mos. later	Asymptomatic restriction 1 yr. X-ray healed scar
2.	M. G.	34	M.	3 years	Deformed Cap. Delayed emptying time	82	90	8 weeks	32	38	Cap. more scarred. No retention	Asymptomatic restriction 1½ yrs. save for epigastric discomfort, promptly relieved by 1 gm. resin
3.	C. M.	39	M.	2 weeks	Duod. spasm and irregularity. Delayed emptying time	88	100	6 weeks	50	60	Smooth Cap. No retention. No spasm on fluroscopy	Asymptomatic 8 mos.; 17 mos. X-ray, healed duod. ulcer
4.	J. G.	44	M.	7 years	Duod. niche gastric retention			12 weeks	20	30	Niche barely perceptible. No retention	Asymptomatic 6 mos. Recurrence of symptoms after 13 mos. Resin reinstituted.
5.	I. G.	38	M.	3½ years	Deformed Cap. Large retention Hemorrhage 1 month prior.			12 weeks	x	x	No retention	All pain disappeared within 4 days of onset of therapy. Remained asymptomatic 1 mo. after discontinuance; then pain recurred, was again relieved after few days and remained asymptomatic 4 mos. while on medication. Patient showed markedly neurotic trends.
6.	H. K.	29	M.	3 months	Deformed Cap. Tarry stools	80		4 weeks	28 repeat 30	40 40	Cap. unaltered	Asymptomatic save for epigastric distress relieved by resin, 7 mos., no blood in stool.
7.	R. S.	38	M.	15 months	Duod. Ulcer	57	62	5 weeks	30	36	Crater not seen, cap. scarred.	Asymptomatic 1 yr. No occult blood. Hypertension.
8.	B. H.	46	M.	5½ years	Deformed Cap. Marked retention	90	104	11 days	x	x	No retention	Asymptomatic at once. Symptoms returned with severe alcoholic bout. Treatment discontinued because of refusal even to mitigate use of alcohol. Gastrectomy.
9.	L. K.	36	M.	2 months	Multiple niches (3) 1 cm apart	92	100	4 weeks			No visible niche, slight scarring	Asymptomatic, 8 months
10.	W. K.	41	F.	1½ years	Pyloric Ulcer	83	90	4 weeks	40	50	No visible niche, moderate scarring	Asymptomatic, 1 year
11.	Z.	47	F.	2 years	Prepyloric ulcer, slight retention	48	54	2 weeks			No change	No relief of symptoms on this or previous rigid Sippy regimen. Marked neurotic factors.
12.	E. W.	43	F.	Many years	Marginal-ulcer			2 months			No change	No relief of symptoms. Marked neurotic factors in this divorcee that did not yield to prolonged psychotherapy following discontinuance of resin.
13.	F. R.	29	M.	2½ years	Deformed Cap. Tarry stools	70	82	8 weeks	30	40	No change	Asymptomatic save for occasional epigastric distress when excited; 4 mos. stools devoid of blood. Sudden severe melena in 6th mo., shock, surgery. A known mental case, borderline institutional.
14.	K.	45	M.	6 years	Deformed Cap. Lost 16 lbs. in 2 years	78	94	5 months	30	38	No change	Asymptomatic, gained 10 ibs. in 9 months.
15.	F.	28	M.	8 months	Prepyloric niche	52	60	4 weeks	22	32	Niche barely visible	Asymptomatic 1 yr. No symptoms after 19 months.

16.	F.	54	M.	More than 14 years	Scarred Cap. Marked retention.	70	80	5 weeks	28	40		Vomiting continued. Developed tarry stools. Surgery for obstruction.
17.	S.	33	M.	2½ years	Pyloric niche	80	92	4 weeks	36	48	Niche not visible. Pylorus scarred from 2 prob. ulcers	Rare transient slight epigast. distress 6 mos. Had eliminated only coffee from diet, still taking spicy foods.
18.	K.	38	M.	3 years	Duo. spasm. Gastric retention	72	90	6 weeks	14	24	Healed ulcer	Asymptomatic, 6 months
19.	H.	44	M.	3 years	Irregular Cap.	64	70	3 weeks	12	28		Asymptomatic, 5 months.
20.	W.	53	F.	2 years	Irregular Cap. Hyperperistalsis	52	64	6 months	10	22	Cap. scarred along lower medial angle. No peristalsis.	Asymptomatic, 2 years.
21.	J. M.	37	M.	8 years	Penetrating Prepyloric ulcer	64	72	1 year	*18	32	Scar at ulcer site, no niche	Asymptomatic 2½ years; has taken no resin in 1½ yrs. No food restrictions. Smokes moderately.
22.	A. G.	39	M.	6 years	Duodenal niche Retention	72	90	2 months	34	42	Healed ulcer	Asymptomatic, 6 months.
23.	J. F.	50	M.	4 years	Duodenal niche	84	100	8 months	*20	32	Slight scarring of cap.	Asymptomatic despite complete disregard of all food restrictions. Had paroxysmal tachycardia prior to therapy; no attacks since on resin.
24.	M. A.	47	M.	3 years	Duodenal niche	Refused		6 months			Healed ulcer	Asymptomatic 1½ years. Had massive heamatemesis 6 mos. prior to therapy; no blood in stools while under observation. Has lumbosacral Pagets Disease.
25.	M. T.	48	M.	6 years	Prepyloric niche	86	140	5 months	*30	42	Niche much diminished (1/4 size)	Asymptomatic 8 mos. Surgery excision for massive hematemesis. Resin therapy resumed after convalescence; asymptomatic, 6 mos. Total duration absence of symptoms while under therapy 14 mos. No dietary restrictions. Smokes heavily.
26.	A. T.	32	M.	3 years	Irregular Cap.	62	88	6 months irregularly	*26	34	No change	All night pain gone, 13 mos. Occ. epigastric distress when under tension. Marked psychosomatic factors and many phobias.
27.	A. C.	40	F.	9 years	Duodenal niche 20% retention	80	120	7 months	*26	40	No visible niche Scarred bulb, no retention	Asymptomatic 7 mos., still on therapy. No dietary restrictions. Smokes 1 pk. cg. daily. Surgery had been advised after failure of Sippey, protein hydrolytes, Larostidin, etc.
28.	M. E.	54	F.	3 years	Spasm of Cap. Diverticulum of 2nd portion	78	92	1 year	*30	36	Duod. spasm absent, cap. smooth. Diverticulum unchanged	Asymptomatic and on resin 1 yr. No food restrictions. Had had intragastric drip therapy without results 3 mos. prior to resin therapy.
29.	A. G.	46	M.	Unknown	Irregularity of Cap. Questionable niche	86	98	4 months irregularly	*20	32	Cap smooth. No visible niche	Asymptomatic 8 mos. Onset with syncope and melena; no blood in stool since therapy.
30.	L. C.	28	M.	2 years	Marked irregularity of Cap.	74	92	1½ years	*18	26	Cap. smooth; no hyperperistalsis	Asymptomatic 16 months.

*Analyses taken 6 months after cessation of all therapy.

ILLUSTRATIVE CASE REPORT

(Case No. 21, Table 1)

J. M., a married white male of 37, is the executive in charge of production of an exceedingly large, nationally known textile firm. For some eight years he was known to have a large prepyloric ulcer from which he had temporary symptom-relief only when he adhered to a rigid bland diet, never less than of six feedings daily. This regimen was accompanied by continuous antacid therapy ranging from soda bicarbonate to amphojel in doses of from 2 to 4 grams at each feeding, and supplemented by frequent resorts to soda bicarbonate

between meals. Despite this, he had never been totally free of abdominal discomfort, considering it "a good day when I am not awakened more than once nightly from sleep by pain." He had a number of severe exacerbations of pain, on two occasions the abdominal tenderness and spasm suggesting the possibility of impending perforation when he digressed, however slightly, from the rigid diet. Operative intervention was suggested at least on one occasion, only the amelioration of symptoms and subsidence of the spasm upon complete bed rest and rigid milk-cream feedings obviating such intervention. As the result of these experiences, he had, for the last 4 years of this period, eaten no meat or leafy vegetables, and had partaken of no tea or coffee. Despite these precautions, and the total abstinence from liquor and tobacco, he had remained with recurrent epigastric pain or distress so frequent that "until I had eaten several times by noon, I was in a mood that made people wary of me and this included my infant son, of whom I am extremely fond."

He was first seen by us on February 14, 1948, at which time he was in excruciating pain and exhibited severe tenderness and voluntary spasm of the epigastrium and upper rectus muscle. At this examination he stated that, if deemed advisable, he would undergo surgery at once. He was given 2 grams of Deacidite, with a little water, in the office. Within three minutes the pain had totally disappeared, as did the abdominal spasm; the epigastric tenderness remained, but was apparently less marked.

Deacidite was continued in doses of one gram every 2 hours and that night, for the first time in almost 6 years, he slept uninterruptedly. For the next two days the medication was discontinued, with return of marked abdominal pain, in order to obtain a gastric analysis. This showed:

Free acid—64 units
Total acid—72 units

Radiographic examination disclosed a large penetrating prepyloric ulcer on the lesser gastric curvature, with retention of barium within the ulcer of about 30% in the 6 hour film, and a pronounced gastric hyperperistalsis but moderately delayed emptying time.

He was placed on a regimen of three meals daily with no restrictions save for the elimination of spicy, fatty, fried or greasy foods. Deacidite was administered in doses of one gram 10 minutes before, and 2 grams 20 minutes after each meal, and 2 grams at bed time. No supplementary feedings were utilized. Alcohol and tobacco were interdicted.

On this regimen the abdominal pain totally disappeared within 3 days, and the epigastric tenderness, both superficial and deep, could no longer be elicited on the 6th day. He slept soundly and uninterruptedly throughout the night. After 2 months he volunteered the information that his grumpy, bear-like personality had actually changed "because I'm no longer in pain and sleep well, people now do not have to wait until noon to do business with me, and I wake up without a grouch." After 12 months of this regimen—and he admitted rather frequent breaches by indulgence in "Chinese" food, occasional alcoholic beverages, and more than occasional cigarettes—Deacidite therapy was discontinued for 6 months. Gastric analysis then revealed the following:

Free Acid—18 units
Total Acid—32 units

Radiologic examination now disclosed scarring at the previous ulcer site. The niche had totally disappeared; there was no disturbance of peristalsis or motility, and no gastric retention. He remained totally symptom-free during this period and the year thereafter, without further therapy or dietary restriction save as suggested but as adhered to in the breach as noted above.

Helped though he was clinically throughout this period, he himself made a significant observation when he remarked that "only after I had gone through 2 of our hectic seasons—and our business, as you know, is a very seasonal and intensive one, with uncertain and hazardous style production risks—without the slightest pain was I fully convinced of my improvement. Though I know that ulcers are supposed never totally to be cured, I think mine is gone for good. He still keeps the Deacidite at home and at his office, but has not taken any for well over 1½ years.

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NUTRITIONAL SUBSTITUTION THERAPY: A NEW METHOD WHICH PREVENTS PROSTATIC SURGERY IN BENIGN PHYSIOLOGICAL HYPERTROPHY: A PRELIMINARY REPORT

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ONE OF THE most common diseases in the male past the fourth decade is benign prostatic hypertrophy (1). Statistics, although limited, show that up to 55 per cent of human males who reach the age of sixty develop some signs and symptoms of prostatic obstruction (2), and of these men about 50 per cent eventually have to undergo prostatic surgery. The purpose of this communication is to describe a therapeutic approach which prevents or retards benign prostatic hypertrophy, thereby eliminating the necessity for surgery.

The role of the endocrine glands, especially the hypophysis and the gonads, in the control of prostatic function has been established. Investigators, early in the twentieth century believed that benign prostatic hypertrophy was mainly due to the testicular hormones. This led to an avalanche of orchectomies, but the procedure was soon abandoned because of its failure to effect a cure. The knowledge of endocrine physiology at that time was fragmentary.

It has since been established in experimental animals that castration increases the gonadotropic activity of the anterior lobe of the pituitary gland. It is also known that although castration eliminates the testicular supply of androgen, it does not eliminate all androgen secretion. Other sources, particularly the adrenals are stimulated and their androgen production may be increased.

Recently, several investigators have shown that male androgen can be inactivated by the female estrogen. It was Huggins (3) and his associates in 1941 who first utilized this knowledge in the treatment of prostatic carcinoma. They observed that some types of prostatic cancer were extremely sensitive to androgens which activated their growth. They also noted that by the administration of estrogens or by castration, or both, they inactivated the androgens and thus succeeded in slowing up the malignant growth. The favorable influence of estrogens in these cases is explained by their depressing effect on the gonadotropic activity of the pituitary gland.

It is our conviction that the knowledge of hormonal and nutritional physiology and pathology gained over the years can also be successfully applied in the prevention and treatment of benign prostatic hypertrophy. Study of these patients reveals an endocrine imbalance and a physiological disturbance which, in a large proportion of cases can be corrected.

By corrected we mean the re-establishment of normal physiological balance. This implies the maximum normal function of all metabolic processes. It therefore necessitates a normal intake of the fundamental carbohydrates, proteins and fats; as well as accessory food factors, vitamins, hormones, amino acids and enzymes; essential minerals, and water. In his publications since 1941 (4) the author has repeatedly emphasized the importance of the synergistic activity of hormones and vitamins in the therapeutic attainment of physiological balance. He has further shown that infection, emotional upsets and mechanical interference with food intake act as serious road blocks, which must be removed or eliminated from the path towards maximum metabolic function and a normal nutritional state.

In a series of publications (5) dealing with vitamins and hormones in normal nutrition, infection was shown to be the main cause of nutritional disturbance in 60 per cent of a series of 200 cases. The most prevalent focus of infection in a large proportion of the male patients in this series was in the prostate gland. Along with the infection there were definite hormonal dyscrasias and vitamin deficiencies,—a constantly concomitant triad of findings. Not until active foci of infection were cleared and judicious diet and replacement therapy instituted could a normal nutritional state be restored.

For this report we have focused our attention on the impressive results we have obtained in many patients in whom benign prostatic hypertrophy was present. We selected for our study 100 cases from a total of 500 (6). The age range was from 15-75 years, with the majority in the 43-63 year old group. In the total series there were many cases whose prostatic disturbances started as early as age 35. In 70 per cent the operative stage of prostatic hypertrophy was prevented. Early prostatic symptoms had developed in 20 per cent, but by replacement therapy and prostatic massages the gland was restored to a normally physiological state. Of the remaining cases 7 per cent had started but did not follow through with therapy, and 3 per cent were considered too far advanced for preventative treatment.

Along with the 7 per cent of cases who started but did not continue therapy a further group of 100 cases, in the same age range, were followed as a control group. Of these control cases 58 per cent required surgical intervention because of advanced obstructive symptoms caused by a benign hypertrophied prostate gland, 16 per cent of these cases having to be treated as acute surgical emergencies. Of the remaining 42 per cent, 8 per cent developed acute prostatic obstruction, but were carried along with frequent catheterization, performed by the patient himself or his local physician.

Because the therapeutic approach we are about to describe is primarily preventative, treatment should be started early, preferably in the third decade of life. Even in teen aged patients with an unusual series of systemic infections, prostatic involvement is so often encountered that therapy should be instituted without delay. The younger the patient, and we have had a few

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While the prostate gland is not a part of the digestive tract, this paper's importance for us is its emphasis on the tie-up between infection and nutrition, as well as the influence of hormones in nutrition. Editor.

patients 15-17 years of age, the easier to re-establish an essentially normal status and to maintain it. Maintenance therapy is sometimes required for a long time.

The importance of complete study of these cases undergoing substitution therapy has been stressed in previous communications (5), but bears repeating. Complete and detailed history should be obtained, including complete systemic histories; history of past illnesses and associated growth and weight variations. Particular attention should be paid to any variations from the so-called normal. Physical examination should be complete and detailed, noting not only gross changes, but even minute changes in the skin, hair and mucous membranes. Careful examination of the prostate should be made, for size, firmness, bogginess, irregularities, nodules and conture. With this, digital rectal examination for rectal pathology should always be done, and where indicated should be followed by proctoscopic or sigmoidoscopic examination.

For routine cases the following laboratory data will usually prove adequate: complete blood counts and differential smear, complete urine analysis preferably of a twelve hour night specimen, fasting blood sugar, nonprotein nitrogen and blood cholesterol. Basal metabolic tests are essential, including at least two determinations, and bearing in mind the significance of temperature, pulse, and bilateral blood pressure at basal levels. Prostatic smears for microscopic examination are obtained whenever possible after every massage. The smears are fixed and stained with Greenberg (7) stain. Trained laboratory technicians study these smears for the usual morphology, cellular debris, sperm, red and white blood cells, and mucus. Each smear is reported in accurate counts of white blood cells present per high powered field.

In this preliminary report, 4 cases will be described in some detail, selected to represent four age groups: an early case, age 20, where the preventative approach would seem to have assured potection againts prostatic hypertrophy in later life; a 35 year old patient who was followed for five years at which time it was felt that benign hypertrophy had been arrested and surgery prevented; a 55 year old patient for whom surgery had been recommended as the only therapeutic measure, but who nevertheless responded to replacement therapy without surgery; and a 71 year old patient who eighteen years previously had refused replacement therapy, and who recently came to prostatic surgery.

Case 1. In addition to the prostatic picture, the following case demontrates that no matter how normal the history may appear, the slight physical and laboratory changes revealed can still add up to serious physical disability, in a young male in the second decade of life.

A 20 year old college freshman complained of anorexia, pain in the lower extremities, and migraine headaches. The history revealed that the headaches had begun six years before, anorexin had come on six months later, and pain in the extremities eight months later. No history of severe infection at the time of the onset of complaints could be elicited.

Detailed past history revealed frequent upper respiratory infections, tonsillectomy two months previous to the onset of anorexia. A few weeks after the tonsillectomy the patient had lost his mother. This information pointed like a beacon to the usual triad. First, endocrine imbalance, indicated by headaches which came on at puberty, age 14, associated with acne, and further emphasized by post adolescent weight gain from ages 13-16. Second, infection, as shown by the history of frequent upper respiratory infections, and by the tonsillectomy which undoubtedly flared up other latent foci of infection. Third, vitamin deficiency, revealed by the symptom of anorexia with its resultant decreased food intake. The emotional upset caused by the death of the patient's mother, and the trauma of the tonsillectomy were important contributing factors which were considered in arriving at a preliminary diagnosis.

Physical examination revealed few gross positive findings. Slight changes were found, such as dryness and loss of luster of the hair, edema with redness of the eyelids, a coated tongue with atrophic papillae, leukoplakin of the mucous membranes, slight increase in heart measurements, a barely palpable liver, thickening with some tenderness in the left epididymis, a dry skin studded by acneform lesions, brittle and ridged fingernails, and lastly a large boggy prostate with no nodules.

Laboratory data were within normal limits, but not, however, at the levels which should be expected for a healthy 20 year old male. Hemoglobin was 13.2 gm. (87%), red blood cell count 4,380,000, white blood cell count 7650, and differential smear showed a relative lymphocytosis. Urine was essentially negative except for a high specific gravity and a sediment showing 6-8 white blood cells and occasional red blood cells in each high powered field. Blood chemistries were normal. Basal metabolic rate was minus 18 per cent.

There had been no history of venereal or other infections which could point to prostatic involvement. Perhaps those innocent upper respiratory infections, or possibly the tonsillectomy, had stimulated this focus of infection. It is sufficient to state, however, that prostatic smears at first showed only debris, but later were loaded with pus cells. In the author's clinical experience many young men in this same age group have received prostatic massages over a period of three to eight consecutive weeks. But at no time did smears show more than 4-5 pus cells per high powered field, followed by at least three smears which showed 2 or less pus cells per high powered field. In the case under consideration, therefore, smears loaded with pus cells were of extreme significance and indicated a prostatic focus of infection.

In this case is an illustration of the careful and detailed history and physical examination which was required in order to establish symptoms and signs which could be closely tied up with nutritional deficiency. It also revealed but a few positive physical findings such as would be expected in a nutritional upset, and only minute laboratory changes when compared to the levels expected in a normal healthy male. Yet these findings, added together, were found to dovetail, and presented a typical vitamin hormone deficiency picture, complicated by the prostatic focus of infection.

Treatment consisted of nutritional substitution therapy. For the endocrine dyscrasia thyroid extract 0.065 Gm. and diethylstilbestrol enteric coated 0.1 mg. was given. Vitamin substitution therapy included a potent elixir of the whole vitamin B complex, a multiple vitamin capsule containing vitamins A, C, D, E, and the vitamin B complex. A full and well balanced diet was outlined. A specific was also given orally for the temporary relief of migraine headaches. It contained ergotamine tartrate, atropine derivative, and a small amount of phenobarbital.

Parenteral injections were given twice a week, consisting of anterior pituitary like hormone in dosage of 250-1000 units; a-estradiol benzoate 0.2-0.6 mg; testosterone propionate or water soluble testosterone 6.0-100 mg.; thiamine chloride 100-300 mg.; deproteinated insulin free pancreatic extract 2-3 cc.; pyridoxine hydrochloride 50-100 mg.; riboflavin 10-20 mg.; and a solution containing the whole vitamin B complex with ascorbic acid 500 mg. given intravenously.

The method was as follows. The female hormone was given in a ratio of 3:1 or 4:1 with the male hormone, that is, the female hormone was given three or four times successively, then the male hormone once. Each dose was given in combination with crude liver extract 1 cc. Anterior pituitary like hormone was given once a week subcutaneously. Thiamine chloride, combined with either deproteinated insulin free pancreatic extract, or pyridoxine hydrochloride, was given once per week intramuscularly. The whole vitamin B complex with ascorbic acid was given at each injection in combination with riboflavin, and administered intravenously. The patient was also given a course of dihydroergotamine methanesulfonate (D. H. E. 45) 0.5-1 cc. subcutaneously once or twice

per week, depending on the frequency of migraine attacks. Prostatic massages were done once per week.

Prostatic smears began to show a greater number of clumps and individual pus cells after oral and mouth substitution therapy had been continued over a four to five week period. This observation has been constant in most of these cases.

After six weeks of this regime, parenteral treatment was reduced to once per week and prostatic massages to once in two weeks. Four weeks later injections and massages were reduced to once in two weeks for six more weeks. The last three prostatic smears were negative for pus cells. Examination of the prostate at this time revealed a gland that was normal in size, soft, and a median sulcus that was easily defined. The thickening that had been present in the upper poles of the epididymis had completely disappeared.

Parenteral therapy was continued over ten more weeks, but with a gradual reduction in total dosage. After completing six months of treatment the patient felt well except for mild headaches unrelated to the migraine syndrome. He had gained 12 pounds in weight. Modified oral medications were continued, with check-up examinations at six month intervals.

The presence of an infectious focus in the prostate in a young, 20 year old male is demonstrated in this case. No other foci of infection were found except for a mild sinusitis. It is apparent that this innocent prostatic infection was the hidden focus which had been the cause of a vitamin hormone dyscrasia with resultant nutritional upset. It was further shown that by complete replacement therapy plus prostatic massage it was possible to approximate normal physiological balance, eradicate prostatic infection, and forestall an early prostatic hypertrophy.

The young man is now a senior at college, and has been under observation for four years. He is still taking his oral medications as outlined, except for the ergotamine tartrate combination which is no longer needed. A series of three booster courses of parenteral therapy and occasional prostatic massages have been given over this four year period. Routine check-up examinations are at six month intervals, and it is hoped that this patient has been brought to realize their significance and importance to such an extent that he will continue with them throughout his life. On the basis of clinical experience it can be predicted that this patient will never suffer from prostatic hypertrophy, barring acute infections.

Case 2. This patient is a relatively young man who started treatment at age 35, and carried over a five year period to age 40. A 35 year old, single, plumber's helper at the time of consultation, complained chiefly of extreme sluggishness and fatigue of five years' duration, complicated by gastric distress which had existed from childhood. The patient could not remember a single period of even six months since age 5 when he had been free from acute episodes of distention and abdominal pain, associated at times with nausea and vomiting, at other times with diarrhea. He had always slept propped up on at least three pillows, because, as he stated, "My chest seems to be filled with gas."

During the past five years he had noticed marked increase in fatigue and sluggishness. Within this same period he had served for twenty-five months in the United States Army, and he stated that nearly half of this time had been spent in dispensaries and field hospitals, always with the same constant complaint of gastric distress. Three gastrointestinal x-ray series had been done by the Army Medical Service each with gallbladder tests, and in addition two barium enemas. All reports had been negative, and he was finally branded by the Army Medical Service as psychosomatic. After discharge from the Army the complaints of fatigue and sluggishness had increased, so that he was able to work only two or three days of his five day working week. He complained further of constipation and some headaches. These headaches, prior to his period of military service had apparently constituted a typical migraine syndrome, but during his military service the syndrome had subsided. The headaches occurred through the frontal region, at times involving the left or right occipital region, but not associated with scotomata, nausea or vomiting. During the last year he had complained of some burning and itching of the eyelids, variable joint pains, and some paresthesias of the fingers and toes. Immediately after leaving service he had lost 10 pounds in weight. During the intervening two years he had not only regained this, but had added 6 more pounds. He had noted increased coldness of the hands and feet, and marked dryness of the skin and hair. His hair had started to turn gray at age 12, increased during his twenties, and was much more marked during the past five years, with rapid change in the past year. His family history revealed premature grayness in both parents. Past history was entirely irrelevant except for bilateral lobar pneumonia six years before.

At physical examination the findings were as follows. Height 69¾ inches; weight 169½ pounds; basal temperature 97.7 F.; pulse 66; respirations 12. The general examination revealed a well developed, fairly well nourished, moderately alert male. The hair was brown, intermingled with achromotrichia throughout, dry, with loss of luster and frontal-parietal recession. Through the temporal region and portions of the anterior occipital region the hair was white. The scalp was dry and somewhat scaly. There was two plus edema of the eyelids, with redness, swelling and some scaling of the contact edges, and white mucus in both the internal and external canthi of the eyelids. Ophthalmoscopic examination was negative except for considerable tortuosity and slight calibre changes of the blood vessels. There was slight deviation of the nasal septum to the left, with hypertrophy and blanching of the inferior turbinates. The mucous membranes of the mouth showed fine leukoplakia throughout. The teeth were in good condition, with considerable dentistry. There was slight edema of the gums and some recession. The tongue was slightly coated, smooth, with atrophic changes of the papillae at the tip and lateral borders. The pharynx showed moderate follicular hypertrophy, some redness, and slight postnasal drip. The anterior and posterior chain glands of the neck were enlarged and palpable. There was limited but equal expansion and excursion of the chest which was somewhat barrel shaped. Rachitic depression of the sternum and manubrium sternum was observed, but no rosary. The apex of the heart was palpable at the fifth interspace, 10cm. to the left of the midsternal line. The left border was percussed at 9.5 cm. to the left of the midsternal line, and 2 cm. to the right. Percussion at the base of the heart in the region of the great vessels was 5 cm. Heart sounds were distant, of fair quality and regular, rate 60. The first mitral sound was slightly accentuated. The second aortic and second pulmonic sounds were equal but extremely distant. There were no murmurs. Blood pressure was 100 systolic over 72 diastolic at basal level. After the basal metabolic test the blood pressure was 92 systolic over 58 diastolic on the right arm, and 98 systolic over 68 diastolic on the left. After coffee the blood pressure on the right arm was 108 systolic over 68 diastolic. Lungs were essentially negative except for an area the size of a silver dollar at the right posterior axillary line which had numerous crepitant rales, more marked after coughing. The patient was just recovering from a mild upper respiratory infection. The abdomen was rounded and soft, with voluntary hyperesthesia. The liver was just palpable at the costal margin. There was slight umbilical herniation and slight widening of the inguinal rings bilaterally. Rectal examination revealed a tight sphincter with tiny internal nonthrombotic hemorrhoids. The prostate gland was markedly boggy, and the median sulcus was barely discernible. The gland, though generally spongy, showed a rather firm area in the left lobe. Notation was made to watch this lobe carefully for a question of malignancy, as the consistency at that time was not definite. The skin was markedly thickened, with superficial dryness, and numerous pigmented nevi. There were many scars from traumatic lacerations. The extremities were cold. Dorsalis pedis and posterior tibial pulsations were sluggish. Toenails were thickened and rigid with evidence of fungus involvement superimposed which extended to involve the interdigital areas between the toes. There were Heberden's nodes of the interphalangeal joints of the fingers and toes. The fingernails were fairly firm, but ridged. Reflexes were sluggish in the upper extremities, slightly exaggerated in the lower extremities, and abdominal reflexes were diminished. No pathological reflexes were elicited.

Laboratory data under basal conditions were as follows. Basal metabolic rate minus 12 per cent. Urine analysis: yellow, clear; acid reaction; specific gravity 1.019; albumen and sugar negative. Microscopic examination of the urinary sediment: occasional squamous cell, rare uric acid crystal, occasional bacteria, rare yeast cell, 6-8 white blood cells per high powered field. Blood tests: hemoglobin 15.5 gm. (102%), red blood cell count 5,000,000 white blood cell count 6700.

Differential smear: polymorphonuclears 50%, lymphocytes 42%, monocytes 4%, eosinophils 4%. The morphology and platelets were normal. Blood Hinton test was negative. Fasting blood sugar 95 mg.%. Fasting nonprotein nitrogen 34 mg.%.

Treatment consisted of complete nutritional substitution therapy. For the endocrine dyscrasia oral medications were the following: thyroid extract 0.065 Gm. twice per day, and diethylstilbestrol enteric coated 0.1 mg. on arising. Oral medication for the vitamin deficiency consisted of a potent elixir of the whole vitamin B complex containing the fat soluble vitamins A, D, E, in a partially water soluble form, along with vitamin C; a capsule containing the fat soluble chlorophyll complex from alfalfa, buckwheat and soybean, 0.38 Gm. three times per day with meals; a tablet of para-aminobenzoic acid 100 mg. four times daily with meals and at bedtime; a tablet containing ketocholanic acids 250 mg. two hours after dinner. These oral vitamin factors were given as a supplement to a 1500 calorie diet, well balanced as to essential nutrients.

Parenteral therapy was given once per week, consisting of the following: anterior pituitary like hormone, a-estradiol benzoate, testosterone propionate, thiamine chloride, deproteinated insulin free pancreatic extract, and crude liver extract. A whole vitamin B complex dissolved in a dilutant of 500 mg. of ascorbic acid, to which was added 10 mg. of riboflavin, was given intravenously. Prostatic massages were given once per week. Prostatic smears examined microscopically were as follows.

No. 1. 10-15 pus cells per high powered field. No. 2. 30-50 pus cells per high powered field. No. 3. 25-50 pus cells per high powered field. No. 4. 25-50 pus cells per high powered field.

At check-up examination four weeks later there was definite improvement in this patient's subjective symptoms, and in his physical and laboratory findings. The same regime of therapy was followed, but after two more months injections and massages were reduced to once in two weeks for the next three months. Prostatic smears, when obtained, over this five month period were as follows.

Weekly massages

No. 1. 10-25 pus cells per high powered field. No. 2 5-10 pus cells per high powered field. No. 3. 5-10 pus cells per high powered field. No. 4. 10-15 pus cells per high powered field. No. 5. 5-10 pus cells per high powered field. No. 6. 10-20 pus cells per high powered field. No. 7. 5-10 pus cells per high powered field. No. 8. 10-15 pus cells per high powered field. No. 9. 5-10 pus cells per high powered field.

Bi-weekly massages

No. 1. 3 pus cells per 30 high powered field. No. 2. 10-15 pus cells per high powered field. No. 3. 1-3 pus cells per high powered field.

During the next two months four more prostatic massages were done, the last three showing not over 3 pus cells per high powered field. It has been the routine in this replacement therapy for benign prostatic hypertrophy to obtain at least three consecutive smears of 3 pus cells or less per high powered field, over a minimum six week period, as an indication that the gland has been cleared of pus. Should the patient develop any intercurrent infection during this time, a new six week period must be started from the time of the acute infection. Injections and massages were omitted after the three so called negative smears had been obtained, and the patient continued on oral medications alone until his next check-up examination four months later.

At this time, twelve months after the start of therapy, his general condition showed great improvement, and many of the subjective complaints had subsided. He was more alert, and was happy to report that it had been more than eight months since he had noticed any gastric complaints. Joint pains had entirely vanished, and he no longer complained of coldness of the hands and feet, nor of any paresthesias. He had lost 12¼ pounds over the twelve month period. He had observed improved moisture and texture of his hair, and reported smilingly that many new hairs had come in completely brown in color, with a general yellow hue throughout the gray hair. He had not been absent from work for a single day over the past seven months.

At physical examination the findings were as follows. Weight 157¾ pounds; basal temperature 97.8 F.; pulse 72; respirations 12. Improvement in the hair nutrition has already been mentioned. The scalp was more moist. There was no edema of the eyelids, and the blepharitis had entirely cleared. Examination of the ocular fundi showed greater dilatation of the blood vessels and very slight evidence of narrowing. Nasal examination showed good color, and definite shrinking in the previously noted hypertrophy of the inferior turbinates. Mucous membranes of the mouth were moist, and there were only slight areas of residual leukoplakia. Gums were normal. Lingual papillae were more pronounced. Follicular hypertrophy in the pharynx was less marked, and there was no postnasal drip. There was greater expansion and excursion of the chest. Heart measurements showed a reduction of 2 cm. in the transverse diameter, and 0.5 cm. in the region of the great vessels. The sounds were more forceful and of better quality, the rhythm regular, rate 72. The first mitral sound was still slightly accentuated. Blood pressure was 112 systolic over 74 diastolic at basal level. After the basal metabolic test the blood pressure was 108 systolic over 72 diastolic on the left arm, 106 systolic over 70 diastolic on the right arm. The lungs were entirely normal. The abdomen was soft, and the liver edge could not be palpated. Rectal examination revealed the sphincter relaxed, the internal nonthrombotic hemorrhoids were not palpable. The prostate gland was much smaller, of firm consistency, and the median sulcus was completely palpable. No nodules were felt, and the left lobe which had been marked for careful observation was of normal consistency with no evidence of tumor formation. The skin was more moist and of better tone. Extremities were warmer. Dorsalis pedi and posterior tibials were more forceful. Toenails were firmer and no evidence of fungus infection was found. Fingernails were less ridged. Reflexes were entirely normal.

Laboratory data were as follows. Basal metabolic rate minus 3 per cent. Urine analysis: yellow, clear; acid reaction; specific gravity 1.016; albumen and sugar negative. Sediment: rare squamous cell, occasional uric acid crystals, occasional bacteria, 2-3 white blood cells per high powered field, 3 red blood cells per high powered field. Blood tests: hemoglobin 15.2 gm. (100%), red blood cell count 5,100,000, white blood cell count 8000. Differential smear: polymorphonuclears 64%, lymphocytes 31%, monocytes 3%, eosinophils 2%. Morphology and platelets were normal. Fasting blood sugar 102 mg.%. Nonprotein nitrogen 28 mg. %. Blood cholesterol 215 mg.%. Prostatic smear 5-10 plus cells per high powered field.

At this time the only adjustment in therapy was reduction in thyroid dosage to one tablet per day after breakfast. Because the patient had given a history of an upper respiratory infection and a virus infection during the four month interval up to the time of his present check-up examination, it was decided that a longer booster course of parenteral therapy, and a greater number of prostatic massages was necessary. Therefore, a booster series of parenteral injections along with prostatic massages was given once per week for four weeks, then once in two weeks for four more treatments, and then two more treatments at three week intervals. Prostatic smears were negative after the fourth week.

This patient has gone along comfortably over a five year period, with check-up examinations once in four to six months. Over the last four years he has required six booster courses of parenteral therapy and massages; the first two courses consisting of a series of four injections and massages each, the third course was of eight injections and massages, the fourth and fifth courses six in number, and the last, after five years of therapy, was twelve.

It is significant to note that over the first year of treatment, particular attention was directed to completely clearing the prostate gland of its infection. Thereafter, the object of therapy was to maintain the gland free from infection. It was further important that a physiological balance be maintained as to endocrine, vitamin, and where indicated, amino acid, mineral and water balance.

If infection, no matter how mild, has been reported in the history, or occurs while the patient is under observation, further prostatic involvement should be suspected. Invariably, it has been found that any acute episode, even a slight upper respiratory infection or activation of an acute focus such as an infected tooth, is capable of provoking a flare up of the old prostatic focus. Less therapy is required if the gland is immediately taken care of, but should it remain untreated a secondary superimposed infection will prolong the therapy needed.

Not infrequently, a gland which seems only slightly infected at the primary examination will show much more drainage of pus in the smears after the first six months of therapy. This sudden increase may be somewhat surprising, but should serve as a warning to continue parenteral therapy and massages for a long enough period to establish complete drainage. In these cases it is wise to obtain six rather than three successive negative smears. A good clinical clue to the type of case in which prolonged infection can be anticipated is, for example, the individual who gives a history of having had severe acne at puberty.

The physical size of the gland at the time of examination is a poor indication of the amount of infection present. The most reliable clinical guide for therapy is the pus cell count found in the individual prostatic smears. This laboratory evidence is infallible. Perhaps one of the most difficult statements to retract is the promise made to a patient, after two consecutive negative smears have been obtained, that at his next visit massages will be stopped. Yet the very next smear may show a specimen that is loaded with pus cells. With this in mind caution should be exercised in making any promises to the patient in answer to his query, "When will this be over?" or "How long will this go on?"

There is no question as to the general physical improvement and sense of well being that this patient recognized, but it is interesting to note changes that were observed in the laboratory tests at the end of the first year. The basal metabolic rate improved from a level of minus 12 per cent to minus 3 per cent, with the reading at the end of the five year period a plus 2 per cent. The urine remained entirely normal, with even the 1-3 pus cells that had been seen over the first year completely disappearing. The 3 red blood cells per 30 high powered fields were of no importance, and were not found again. Blood counts showed a decrease in the blood hemoglobin from 15.5 gm. (102%) to 15.2 gm (100%). This is undoubtedly secondary to the improvement in the metabolic state with the concomitant loss of fluids, definitely evident in the loss of ocular edema, improved moisture and tone of the skin, reduction in the size of the heart, increased pulmonary expansion, and decrease in liver size. A significant observation is the change found in the differential blood smear which showed polymorphonuclear cells increased from 50% to 64%, and lymphocytes decreased from 42% to 31%. Of some significance is the drop in eosinophils from 4% to 2%, although in many cases this drop is much greater. The rise in fasting blood sugar from 95 mg.% to 102 mg.% should also be noted.

Improvement in physical findings, although apparently minor, were significant. As mentioned before, these cases are subclinical deficiencies. They are not full blown, classic, textbook cases. Therefore, the variation in all findings are extremely slight, but the minute changes obtained from the history, physical examination and laboratory findings, all add up to establish a diagnosis of subclinical nutritional deficiency.

This patient has been carried through a crucial period in his life, from age 35 to 40. The regime of complete substitution therapy of essential nutritional factors, along with prostatic massages, was entirely responsible for the end result, that is, a physiologically normal prostate gland clear of infection, and without recourse to surgical intervention. Had the patient gone on into his middle or late forties, his early beginning prostatic hypertrophy, so easily remedied at age 35, might have presented a much more serious problem. Complications involving the important organs of the body also might have developed.

Case 3. In contrast to the foregoing cases which were primarily preventative, the next case is one in which the physiological approach by substitution therapy with vitamins and hormones, clearing of foci of infection, and prostatic massage is demonstrated in reverse. This patient had been advised by at least three competent urologists only two months prior to my primary consultation that prostatectomy was urgently needed. His case has been selected for discussion as representative of similar cases in which the patient had had previous urological consultation elsewhere. In this particular case, and in many others, the consulting urologists had been geographically located in all portions of the United States, and included a recognized medical center. It could hardly be questioned that thorough, modern and complete examination had been carried out, nor that the recommendation for surgery must have been indicated. The chief complaint of dribbling and nocturia was the key symptom in this and in similar cases which will be presented in a later, more extensive communication (6).

A 55 year old, white male bachelor executive, with "prostatic syndrome" of ten years' duration, complained also of trigeminal neuralgia and hypertension of five years' duration. Six months before coming to me the patient had an acute attack of "coronary thrombosis" for which he was hospitalized for five weeks. The usual sequelae of attacks of angina pectoris had been present since that time. For the past five months the patient complained of vertex and occipital headaches.

The "prostatic syndrome" consisted of narrowing of the urinary stream, difficulty in starting, dribbling, nocturia 4-6 times, backache, and a drawing sensation through the median aspect of the thighs. During the last five years a competent urologist had performed a series of transurethral curettings at four to six month intervals. These procedures had been carried out in an attempt to overcome the prostatic urethral obstruction. Periods of relief had at first lasted three to four months, but gradually shortened, until the last treatment afforded relief for only three or four days. The patient was then told that there was a residual of 3-4 ounces of urine in the urinary bladder, and therefore prostatectomy was urgently needed. This ultimatum had been delivered two months before the patient's original consultation with me. During the intervening period he had been re-examined by three or more competent urologists who corroborated the necessity for surgical intervention, the last examination having been made only ten days before. During this two month period the patient had gained 10 pounds in weight, was disturbed by more frequent anginal attacks, and had further noted increasing fatigue, periods of depression and irritability.

Physical examination revealed a well developed and well nourished white male, who appeared older than his years. Hair and skin were dry. There was two plus edema of the eyelids, and blepharitis. There were marked arteriosclerotic changes of the retinal vessels. Leukoplakia was present throughout the mucous membranes. The tongue showed atrophic papillae. The heart and blood vessels showed characteristic changes consistent with arteriosclerosis, with a hypertension of 196 systolic over 104 diastolic. A few scattered coarse crepitant rales were found at the bases of the lungs. Through the large obese protuberant abdomen the liver edge could be palpated 2 fingerbreadths below the costal margin. The liver was smooth, nontender. Genitalia revealed a small hydrocele of the left testicle, and an epididymitis at the upper pole of the right testicle. Rectal examination showed external and internal nonthrombotic hemorrhoids, with spasm of the internal sphincter. The prostate was markedly enlarged and boggy, the median sulcus was not palpable, and there were no nodules. Slight peripheral pitting edema was present. Pulsations of the peripheral vessels in the lower extremities were feeble. The nails were ridged and brittle. There was slight coarse tremor of the extended fingers. Reflexes were slightly hyperactive, but none were pathological.

Laboratory data were within normal limits, except for a high specific gravity of the urine, with low nocturnal twelve hour output, and the sediment showing numerous pus cells with many clumps, and 6-8 red blood cells per high powered field. Fasting blood chemistries revealed a slight increase in nonprotein nitrogen and uric acid, and a decrease in blood cholesterol. Electrocardiographic changes were consistent with a hypertensive heart with arteriosclerotic changes in the coronary vessels and evidence of healing in a small posterior right coronary branch.

The findings in this patient were relatively few. Most significant were the slight changes which pointed to endocrine dyscrasia, vitamin deficiency, and the presence of active infection. The patient was obese. There was marked evidence of generalized arteriosclerosis, leukoplakia of the buccal mucous membranes, enlargement of the heart, decreased vital capacity, enlarged liver, dryness of the skin and hair, brittle nails, and poor peripheral vascular pulsation. All these apparently insignificant changes pointed definitely to an endocrine vitamin upset with resultant upset in the nutritional balance.

For the past ten years the patient had been a potential prostatic case, and complained of every classic symptom consistent with prostatic hypertrophy. Yet the urine showed a large number of pus cells and blood cells. There was an in-

crease, although slight, in fasting nonprotein nitrogen and fasting blood sugar. Previous therapy had been concentrated solely on the prostatic obstruction, and more recently on the circulatory accident. Therefore the question arose as to the possibility of the circulatory history and the hypertension being the end result of a chronic infection in the genito-urinary system, plus a nutritional deficiency. By bringing back physiological nutritional balance to as nearly normal levels as possible, and at the same time clearing up the tremendous infection present in the genito-urinary tract, a balance might be established which would relieve all the complaints of this patient. In this approach it was realized that we had two strikes against us: one the vascular accident, and second the possibility of a prostate that had been irritated far beyond the help of substitution therapy. But the patient was so uncomfortable, and so feared surgery, that he was willing to cooperate with any therapeutic approach.

A 1200 calorie diet was prescribed. Oral medications consisted of the following. Endocrine factors: tablet thyroid extract 0.065 Gm. one after breakfast daily, tablet diethylstilbestrol enteric coated 0.1 mg. one daily on arising. Vitamin factors: an elixir of the whole vitamin B complex, 5 cc. with breakfast and dinner, a capsule containing vitamins A, D, C, with some vitamin B complex, taken with breakfast and dinner, a capsule containing vitamin E in the form of mixed tocopherols 150 mg., taken twice daily, on arising and at 5 p.m. A tablet containing ketocholanic acids was taken two hours after dinner, and a tablet containing small doses of atropine, ergotamine tartate, and phenobarbital was taken at 10 a.m. and 9 p.m. A capsule of sodium seconal 0.15 Gm. was given for sleep as needed.

Parenteral therapy was given twice per week, consisting of anterior pituitary like hormone, testosterone propionate, a-estradiol benzoate, ketohydroxystrone, corpus luteum hormone, crude liver extract, thiamine chloride, pyridoxine hydrochloride, riboflavin, deproteinated insulin free pancreatic extract, and a whole vitamin B complex dissolved in 500-1000 mg. of ascorbic acid and given intravenously.

Prostatic massages were given once per week. Smears were reported in counted numbers of pus cells per high powered field. When smears were reported "loaded" the cells were so thick that count was impossible. Smears up to the time of the check-up examination are given below.

No. 1. 13-22 pus cells per high powered field. No. 2. Loaded. No. 3. Loaded. No. 4. Loaded areas.

At check-up examination one month later there was considerable improvement in the general condition with lessening of the headaches and definite improvement in urinary output with increase in the force of the urinary stream and less dribbling. Nocturia occurred only once, or on occasion, twice per night. The urine showed a more normal specific gravity, with 4-6 white blood cells per high powered field, and 1-2 red blood cells per high powered field. The patient continued on the regime as outlined, and six weeks later at his second check-up examination there was further improvement. He had lost 10 pounds in weight, the amount gained in the two months prior to my original consultation. Oral medications remained the same, the parenteral therapy was reduced to once per week, and later to once in ten days. Prostatic massages were continued once per week, and prostatic smears over this period are reported below.

No. 1. Loaded. (Check-up examination one month after beginning therapy). No. 2. Loaded. No. 3. Loaded. No. 4. 3-10 pus cells per high powered field. No. 5. Loaded. No. 6. 5-35 pus cells per high powered field. No. 7. 6-30 pus cells per high powered field. (Ten week check-up). No. 8. Loaded. No. 9. Loaded. No. 10. Loaded. No. 11. 25-75 pus cells per high powered field. No. 12. Loaded. No. 13. 6-50 pus cells per high powered field. No. 14. 9-80 pus cells per high powered field.

Five months after the original consultation, check-up examination revealed marked improvement in both subjective complaints and physical and laboratory findings. The urine showed more normal specific gravity, and the sediment revealed 1-2 white blood cells per high powered field, and no red blood cells. The patient had been free from headaches, complained of no anginal pain, was peppier, slept better, had only rare nocturia. He had lost all the symptoms of his prostatic syndrome, although prostatic smears continued to show loaded or partially loaded smears, with occasional low counts, only to be followed by a loaded smear again.

At this time oral medications were adjusted as follows. Tablet diethylstilbestrol enteric coated 0.1 mg. on alternating mornings on arising. Added to the regime was a tablet of methyltestosterone 10 mg. which was placed under the tongue on arising three mornings per week. This medication was changed with each advance in oral male hormone therapy, until now the patient is taking the most recent tablet, testosterone propionate 5 mg. on alternating mornings on arising. Further additions to the oral regime consisted of a tablet containing hesperidin 50 mg. with ascorbic acid 50 mg., and a capsule containing the fat soluble chlorophyll complex from alfalfa, buckwheat and soybean, 0.38 Gm. each being given three times daily with meals.

At the eight month check-up examination the patient had been entirely free from anginal attacks for a three month period. He had lost considerable weight and with this loss noted that he had no dyspnea on moderate effort as before. He observed also pronounced improvement in his general energy, improved bowel activity, and a marked increase in diurnal urinary output with decrease in nocturnal output. He had experienced no periods of depression, and was much less irritable. His sleep had so improved that in this three month period he had taken only six of the sedative capsules.

Physical examination revealed the following changes. The skin showed improvement in tone and moisture, the hair was more moist. There was definite improvement in the retinal vessels with some dilatation in many of the narrowed branches. The leukoplakia of the mucous membranes had almost entirely cleared, papillae of the tongue were more pronounced. The lungs were entirely clear. The liver was barely palpable at the costal margin, and was much more easily accessible because of the loss in obesity and protuberance present at the primary examination. The epididymitis of the right testicle was markedly decreased. There was no peripheral edema. Pulsations of the peripheral blood vessels of the lower extremities were much more forceful. Reflexes were normal rather than hyperactive. In a word, the general appearance of the patient was twenty years younger. Laboratory findings were all essentially within normal limits.

There had been noticeable improvement in prostatic smears, but an occasional loaded specimen was seen. Smears over this three month period are given below. On examination the prostate gland was much smaller, with no bogginess or nodules, and a widely palpable median sulcus.

No. 1. No smear obtained. (Five month check-up examination). No. 2. 7-60 pus cells per high powered field. No. 3. 2-25 pus cells per high powered field. No. 4. 10-90 pus cells per high powered field. No. 5. 5-50 pus cells per high powered field. No. 6. 10-70 pus cells per high powered field. No. 7. 2-25 pus cells per high powered field. No. 8. Loaded. No. 9. 3-9 pus cells per high powered field. No. 10. Loaded. No. 11. 3-10 pus cells per high powered field.

Parenteral therapy and massages were reduced to once in two weeks. The patient was started on a tablet containing veratrum viride 10 Craw units, four times per day, before breakfast and one hour after breakfast, and before dinner and one hour after dinner. Clinically there was a definite decrease in the hypertension with the diastolic figure consistently below 90 ml. Because of this favorable response to the veratrum viride it was continued, and the tablet containing atropine, ergotamine tartrate and phenobarbitol was omitted.

This patient continues to be checked at four to six month intervals, with adjustment in medications as indicated, and with booster courses of parenteral therapy and prostatic massage. No prostatic surgery has been needed, and will not be required if, and only if, physiological nutritional balance is maintained.

In this case the patient had been receiving urethral dilatation by transurethral curettage and had been told that the prostatic smears were negative. It will be remembered that our first one or two smears also showed very little. However, with the beginning of replacement therapy, smears began to show increased drainage, and after a few weeks were loaded with pus cells. While the foci of infection in the lungs, liver and prostate were being cleared, the metabolic and biochemical processes were adjusted, and the androgen-estrogen balance was being restored. Imbalance of these latter hormones may actually constitute the chief factor in the etiology of benign prostatic hypertrophy. Is it not feasible, therefore, that in reverse, as sex hormone balance is re-established, a gradual reduction in the hypertrophy takes place, with resultant in-

creased drainage of the gland? Histologically, the direct result of this replacement therapy may be the evagination of the deeply buried, infected acini within the prostate gland.

The common practice of massage plus bladder irrigation, as employed by urologists, can not alone be expected to return the prostate gland to a normal physiological state. To restate our premise differently, in the treatment of such prostatic cases it is most important, along with the usual massages, to provide or replace all the essential factors necessary to establish physiological balance. To bring this about all foci of infection must be eradicated, and special attention must be given to the endocrine, vitamin, amino acid, mineral and water balance. In this third case, when mechanical dilatation and curettage was performed it was carried out in a non-sterile field on infected tissues. Trauma to infected areas has long been recognized as a factor in extending infection, with resultant secondary edema. Therefore in this case the curettage probably caused an increase in the size of the obstructing middle lobe, rather than the desired decrease in size. In addition, infected bits of prostatic tissue, or shall we say the debris from surgery, must necessarily have been thrown into the urinary bladder contents. Undoubtedly this procedure was the cause of the markedly infected urine found at the primary examination.

In these cases with severe nutritional and endocrine deficiencies, a tremendous added load is placed on liver function. Measures to relieve this extra burden on the liver and portal circulation can and should be taken. Recent advances in physiology have clarified the many functions carried on by the human liver, each one of which must be helped in giving this type of therapy. For example, in the presence of hepatic infection the storage function of the liver in vitamin metabolism is interfered with, the result being that none of the vitamins in the diet are normally conjugated. Inadequate liver storage also interferes with fat, protein, carbohydrate and hormone metabolism. It is for this reason that in the replacement regime these nutrient elements must be substituted in sufficient surplus amounts, both parenterally and orally, in order to lessen the work of this organ in its storage function. This is continued until normal liver function is restored. It should be repeated that a high caloric, high protein, high vitamin diet must be taken during this entire procedure. Meanwhile, gentle prostatic massage is carried out to enhance drainage of the gland, but with full recognition that all other therapy, parenteral and oral, as just outlined, is essential.

If the necessity for this entire therapeutic procedure, as presented in the above three cases could be fully comprehended, then a great advance in the prevention of prostatic hypertrophy and the elimination of prostatic surgery for physiological hypertrophy of the prostate can be anticipated.

Case 4. The purpose in presenting this fourth case is to describe, in contrast to the preceding cases a patient who had been followed over an eighteen year period but who ultimately had to have a prostatectomy as an emergency measure. At the outset this patient refused to take any preventative treatment, even oral medication.

He was a 71 year old, married accountant, who at the age of 53 was advised that he should have treatment as outlined above in order to avoid prostatic surgery. His prostatic symptoms consisted of urgency, frequency, narrowing of the urinary stream, and nocturia 2-4 times. He gave a history of having been constipated for many years and having become an addict to tablets cascara sagrada nightly for at least a thirty year period. When warned of the danger of constant catharsis of this type, the patient stated that it would be otherwise impossible for him to have a bowel movement. Additional gastrointestinal symptoms consisted of bloating, gas, belching, occasional pyrosis, and the presence of red blood in the stool. In the past year, frontal headaches had become progressively worse. Over a ten year period the patient had gained some 20 pounds, and had noted some dyspnea on moderate effort since weight gain. For six weeks prior to the primary check-up examination he had been coughing intermittently, more marked at night. He had had several episodes of precordial pressure which did not radiate. At times edema of the ankles had been observed. Vertigo, some scotomata, tinnitus aurium, and on rare occasions palpitation were added complaints. The patient stated that he was conscious of the fact that he tired much more easily, and that he had become more irritable during the past few months. His sleep had become restless, partly because of the nocturia. There had been a marked decrease in libido.

Physical examination revealed the following. Height 68½ inches, weight 174¾ pounds. General observation revealed a well developed and well nourished white male. The hair and skin were dry. There was two plus edema of the eyelids with mild blepharitis. There were premature bilateral cataracts. Retinal vessels were markedly sclerosed. Leukoplakia was present throughout the oral mucous membranes. The tongue was badly coated and showed many atrophic papillae. The gums showed many areas of recession. The chest was barrel shaped with limited expansion and excursion. The heart borders were markedly enlarged, consistent with cor bovis. Heart sounds were distant but of fair quality. The rate was 58, rhythm regular. The first mitral sound was moderately accentuated, and the second pulmonic sound was slightly greater than the second aortic sound. Blood pressure was 118 systolic over 78 diastolic. Medium to coarse crepitant rales were heard at both lung bases, increased after cough. The abdomen was large, obese, protuberant. By percussion the liver edge was found to be 3 fingerbreadths below the costal margin. It was smooth and nontender to palpation. There was some tenderness along the entire descending colon. Peristalsis was markedly diminished on auscultation. There was a well healed appendectomy scar. Both testes were atrophic, about 50 per cent of the normal size. There was a slight bilateral epididymitis. Rectal examination revealed large external tabs and thrombotic hemorrhoids. The sphincter was tight, with extreme tenderness when the gloved finger was introduced. There were large thrombotic and nonthrombotic internal hemorrhoids. The prostate gland was markedly enlarged and extremely boggy. The median sulcus was nearly obliterated. No nodules were palpable. The gloved finger showed fresh red blood. There was marked crepitus in the larger joints, and Heberden's nodes of the interphalangeal joints of the fingers. The nails were ridged, peeling and brittle. There was slight coarse tremor of the extended fingers. Reflexes were moderately hyperactive, but none were pathological.

Laboratory data were within normal limits except for high specific gravity of the urine and an increase in nocturnal output. The urinary sediment showed 4-6 white blood cells, and 2-3 red blood cells per high powered field. Fasting blood chemistry revealed a slightly increased blood sugar level with a somewhat elevated nonprotein nitrogen level. The blood cholesterol was moderately elevated. Electrocardiogram showed changes consistent with right ventricular hypertrophy, increased P-R and Q-R-S intervals, intermittent irregularities in the rhythm consistent with arteriosclerotic plaques. The basal metabolic rate was minus 15 per cent.

This patient was extremely apprehensive and suspicious of every step taken in his examination. The nurse and technician had to use great tact to convince him that he would survive the ordeal of venipuncture. Each procedure of the examination and tests had to be explained, and he constantly required reassurance that none would be fatal. In view of this, it is not difficult to appreciate that parenteral therapy and prostatic massage would be impossible to administer.

With much difficulty, and with the promise that he would lose weight, the patient condescended to take some oral medication. This consisted of diethylstilbestrol, enteric coated, 0.1 mg., one tablet on arising; thyroid extract 0.065 Gm. taken daily after breakfast; an elixir of the whole vitamin B complex, 5 cc. with breakfast and dinner; a capsule containing vitamins A, D, C, with some vitamin B complex, taken with breakfast and with dinner; and a capsule containing vitamin E in the form of mixed tocopherols 150 mg. taken twice daily on arising and at 5 p.m. In addition he was placed on a well balanced, low caloric diet.

After a long verbal battle, the patient was finally convinced that he should go to a proctologist for injection therapy for his hemorrhoids. It was only after the threat that surgery otherwise would be necessary that he finally consented. Several months after this he was induced to go to a urologist for a few prostatic massages.

This patient was carried along intermittently over an eighteen year period. He reluctantly admitted that he had been much more comfortable and free from rectal irritation and bleeding after the hemorrhoids had been reduced by injection. He had gone to the urologist at intervals of six to eight months, to face a major ordeal at each massage. He had done well with his dietary regime, and had reduced his weight

to 158 pounds, and had lost his cardiorespiratory symptoms and edema. The prostatic symptoms, however, were not improved even though the urologist induced him to have treatments once a month for a period of a year.

In April 1949 the patient was admitted to the hospital for urethrocystogram, which revealed an unusually large prostate, evidence of about 150 cc. of residual urine, and a moderate size diverticulum of the urinary bladder. A routine examination of the patient's blood chemistry showed a fasting nonprotein nitrogen of 48 mg.%. He was advised by the urologist to have a prostatectomy done immediately, but the patient refused.

After leaving the hospital he went along, with increasing prostatic symptoms, until late in June of 1949, when he reentered the hospital for the first stage operation of a two stage prostatectomy. At this time the nonprotein nitrogen was 56 mg.%, and one week after the first stage operation it rose to 76 mg.%. Because of the severe infection of the bladder and the high nonprotein nitrogen the patient had to be carried on drainage for four weeks. The second stage was finally done late in July when the nonprotein nitrogen had dropped to 38 mg.%.

It should be mentioned that a bilateral high saphenous ligation had been done by a general surgeon just preceding the second stage operation. While the patient was lying in bed considerable peripheral edema of the lower extremities had developed. For this reason, after consultation between the urologist, general surgeon and internist, it was felt that with edema already present, and with the patient facing pelvic surgery, ligation would be a preventative measure against postoperative emboli.

On the third day after the second stage operation the patient went into cardiac decompensation. On the tenth postoperative day he developed broncho-pneumonia. Needless to say the postoperative course was exceedingly rocky, and the patient's life hung on a thread many times during the next ten weeks. It took nearly eighteen months for this patient to regain his strength, put back his tremendous weight loss, build up his low blood levels, and return him to as nearly normal nutritional levels as possible, bearing in mind that much of the damage done had been irreparable.

Had this patient not been so fearful, and started treatment as recommended eighteen years before, he could, in our opinion, have gone along with a normal prostate gland. The therapeutic approach as described could have avoided many of the complications, no upset in the nutritional balance would have occurred, and much of the irreparable damage could have been prevented. A healthier, happier, and undoubtedly younger appearing patient would have resulted.

SUMMARY

1. From a preliminary series of 100 cases of benign prostatic hypertrophy, 4 cases have been selected for detailed discussion, representing age groups from 20-71 years.

2. In 2 of these cases prostatic hypertrophy, itself, was prevented; in the third case surgery had previously been recommended as urgent, but was averted by massages plus complete replacement therapy with vitamins, hormones and amino acids; in contrast, the fourth case refused replacement therapy until too late to prevent surgery.

3. Detailed successful therapeutic measures are described in the first three cases.

4. A control group of 107 cases in a similar age group were followed. Of this group 58 per cent required surgery for acute obstruction due to benign prostatic hypertrophy. Another 8 per cent having acute obstruction were carried along by frequent catheterization.

5. The absolute necessity for restoring physiological balance by nutritional replacement therapy, the importance of eradicating all infectious foci in order to maintain a good nutritional level, and the advisability of follow up examinations with booster courses of parenteral therapy in conjunction with prostatic massage is urgently recommended.

6. By this therapeutic approach a method for prevention of all surgery for simple hypertrophied benign prostatitis is demonstrated and presented for consideration.

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EDITORIALS

DENTAL INFECTION AND HEALTH

Just as medical attention has been increasingly focused upon nutrition, so it has dwelt less and less upon the possible influence of dental focal infection as a primary cause of systemic disease. Easlick (1) in a recent voluminous contribution to the subject of dental infection and its effect on health, shows that dental opinion and medical opinion are both opposed to the theory, started by bacteriologists and clinicians 40 years ago, that dental infection was a common primary source of general disease or ill health.

Certainly the day when an internist of repute would order a *general dental extraction* for any reason has fortunately passed. Teeth which can be used for chewing food are extremely valuable to general nutrition Furthermore, the average physician has been very frequently disappointed in the lack of general results obtained from the extraction of even radiographically infected, or dead teeth. It has been a decidedly hit-and-miss affair, so much so that not a few internists have lost interest in dental infection. Yet it is impossible to read the early contributions of William Hunter on this subject without being persuaded, by his logical demonstrations, that infected teeth frequently exert an important, malign influence on blood formation as well as other physiological functions.

It is undoubtedly important for the internist to have a reliable dental report on every patient in whom the course of illness is obscure. Furthermore, dental infection can unquestionably aggravate such diseases as rheumatoid arthritis by its depressing effect on the whole organism. Then there occur these occasional brilliant results where a neuritis or a frozen shoulder are quickly cured by extraction of a single infected tooth. The theory of dental infection as a cause of ill health has been undoubtedly over-played, but it is a theory which can by no means be completely ignored or discarded.

(1) Easlick, K. A.: An evaluation of the effect of dental foci of infection on health. J. A. Dental Assoc., 42, 6, June 1951.

"EUGLYCEMIA"

The cow who has a continuous digestion presumably has also a pretty constant level of blood sugar. At the moment we cannot think of any really outstanding bovine qualities of mind or body which might be attributed to what might be termed her "euglycemia" (except her milk-production), but nevertheless it is a clinical observation of many physicians that patients sometimes feel better if they abandon the "three squares" and indulge in rather frequent snacks throughout the working day. It is quite possible, as some suspect, that a great many individuals, especially those who suffer hunger pains 3 hours after breakfast or who notice "lag" and fatigue about 4 p.m. are actually experiencing a hypoglycemia, due to insufficient food intake, particularly protein. This can best be determined (where necessary) by the 6 hour glucose tolerance test, although it is a laborious procedure. This test is excellent for picking up the hyperinsulinism people because it is usually only in the 4th to 6th hour samples of blood that the hypoglycemia is discovered.

Perhaps, in a limited sense, we are all more or less capable of hyperinsulinism under certain conditions. The ingestion of high carbohydrate meals or drinks, by producing temporarily a hyperglycemia, stimulates excessive insulin incretion which, in turn, straightway leads to a distressing hypoglycemia with its attending symptoms. Certainly not all who suffer as a result of this simple mechanism have true hyperinsulinism. The latter must be regarded as a pathological and steady production of insulin, whether due to an insuloma or not.

Among these "wrong eaters" are those who complain of what at first sounds like ulcer symptoms, although in these cases no ulcer is to be found by the most careful x-ray examinations. Many of them, if not all, improve at once when they are instructed to eat more protein at all meals and to partake of such articles as milk or unsweetened fruit juice regularly between meals. Admittedly this is good ulcer treatment too, but the feeling grows that some cases of pseudo-ulcer are due to hypoglycemia resulting from too infrequent protein feedings.

Perhaps in a "state of nature" (so different from our stereotyped civilization) meals would be smaller, more frequent, and less sweet. In this ideal state, *homo sapiens* would have nothing to do but hunt, think, enjoy the landscapes and pluck fruit from the trees at his pleasure. He would be relatively free from the constant daily grind requiring continuous application and expenditure of energy. Our present 3 meals-a-day scheme is one solely of convenience and there is no proof whatever to show that it is a perfect scheme.

We know that much of the protein we consume is metabolized into carbohydrate, thus furnishing a moderate increment of energy without over-stimulating the pancreas. Thus, for persons suffering from faintness, mild nausea, hunger pains and weakness midway between breakfast and lunch, the first measure is to institute a breakfast containing bacon, eggs and milk, with a ten o'clock supplement of milk if necessary. The same principles may be applied to all meals and to the periods between lunch and dinner, as well as the hours between dinner and bedtime. We know that such a regime very often solves the patient's difficulties.

One of the reasons for failure to obtain "euglycemia" is the preponderance of carbohydrate in an American diet. Another reason is the American "strenuous life." These basic causes are difficult to overcome. As time passes, the average individual, even in this country, is going to get less and less protein of excellent biological value. The reason is simple—an increasing population on the one hand and relatively fewer meat animals on the other. Under present economic conditions, where so large a fraction of net earnings is consumed in taxes, there is no chance whatever that anyone, from the executive down to the day-laborer, is

going to be able to ease up much in his application to duty.

The good-breakfast campaigns are having considerable influence for good. But many patients need good snacks as well, and it is precisely these hypoglycemic persons who should avoid highly sweetened drinks of all kinds. It we are not mistaken, this conception of "euglycemia" is eventually going to make drastic changes in our selection of foods and the frequency of our eating. Yet there is no reason to attribute everything under the sun to low blood sugar, as some enthusiasts seem inclined to do.

Beaumont S. Cornell, M. D.

A NEW MEDICAL JOURNAL

The President of the American Diabetes Association has just announced (September 26, 1951) the inauguration of their new official Journal, DIABETES, the first bimonthly issue of which will appear in January. This Journal replaces the annual Proceedings and also the Quarterly DIABETES ABSTRACTS, both of which have been published for the past ten years. The Editor is Frank N. Allan, M. D. and the distinguished Editorial Board is headed by Charles H. Best, M. D., co-discoverer of insulin. The original papers and reviews will be prepared for the internist and general practitioner rather than for the diabetes expert. A very complete section on Abstracts will appear in each issue. The subscription cost to non-members of the Association is not stated. We welcome this special Journal and predict it will enjoy a useful and unusually successful career.

ABSTRACTS ON NUTRITION

KERSLEY, G. D., MANDEL, L., JEFFREY, M. R., BENE, E. AND TAYLOR, K. B.: *Hypoglycemia in treatment of rheumatoid arthritis.* Brit. M. J., Sept. 8, 1951, 574-8.

On insulin treatment 82 percent of 72 cases of rheumatoid arthritis improved temporarily, 44 percent markedly so. After 2 months the improved figure had dropped to 58 percent, but seven had progressed to complete remission after 6 months. In a control series, without insulin therapy, but with the same physiotherapy, 78 percent improved, but only 14 percent markedly. The effects of insulin therapy closely resembled the effects of A. C. T. H. treatment. Probably hypoglycemia stimulates the pituitary gland.

KERSLEY, G. D., MANDEL, L., TAYLOR, K. B. AND JEFFREY, M. R.: *Spontaneous hypoglycemia after insulin therapy in rheumatoid arthritis,* Brit. M. J., Sept. 8, 1951, 578-80.

Two patients, being treated by insulin for rheumatoid arthritis, had spontaneous attacks of hypoglycemia following a second course of treatment. The mechanism of these attacks was not elucidated. One of them occurred 12 days after the cessation of insulin. Although such spontaneous attacks of hypoglycemia are rare following insulin therapy, they are easily controlled by a high protein diet and a snack at bedtime, and appear to be harmless.

LEVENSON, S. M. AND EVANS, S. I.: *Nutritional problems of patients with burns.* Nutritional Reviews, 9, 9, Sept. 1951, 257-260.

World War II taught that deep burns, especially of the "wet" necrosis variety, may lead to marked nutritional disturbances. Even it the burned area is very extensive, healing can take place if the patient is maintained in good nutrition and if infection is controlled. The frequent onset of sudden malnutrition brings about serious complications—poor granulations and failure of skin grafts to take. Much remains to be understood about the faulty metabolism in burned patients, e.g., no data are available on the metabolic rate of specific tissues in these cases. Significant protein depletion follows thermal burns, and water and electrolyte changes occur. Serum sodium and chloride are reduced and a negative potassium balance of 2 to 5 g. daily for the first 3 days has been recognized and can be overcome by oral potassium. Gluconeogenesis is increased. There is deficiency in ascorbic acid and in some of the B-complex factors. In severe burns, liver function is depressed. In treatment, high dietary intake is urgent. The treatment of shock with transfusions goes without saying. Nutritional demands should, if possible, be supplied by the mouth, and 50 percent overfeeding should be begun as soon as possible. The use of various hormones including ACTH and Cortisone are under intensive investigation at present.

In radiation injuries little is known about nutritional treatment but persons in good states of nutrition withstand the injuries best.

JOHNSON, H. W. AND RYNEARSON, E. H.: *A diabetic patient on a high fat diet for 29 years without complications.* Proc. Staff Meet. Mayo Clin., 26, 18, Aug. 29, 1951, 329-331.

The patient described was placed on an extremely low protein and carbohydrate diet with large amounts of fat in pre-insulin days in 1921, and although in the interim he had used insulin in varying dosage, he had not, for some unknown reason, ever deviated from his original diet, as altered in 1922. It contained 46 gm. carbohydrate, 50 gm. protein and 254 gm. of fat, a total of 2750 calories. Thus, 83 percent of his diet, or all but 464 of the 2750 calories was made up of fat. Twenty-eight years later he was examined and the neurological and ophthalmoscopic state was found normal. All vessels were open and normal on palpation. There was no albumin in the urine and the values for blood fat were normal. There was no indication of vitamin deficiency in spite of the fact that all vegetables were boiled three times before use. This case certainly shouts defiance to some of the current conceptions in nutrition and was unique in the experience of the authors.

MAY, C. D., SUNDBERG, R. D., SCHAAR, F., LOWE, C. U. AND SALMON, R. J.: *Experimental nutritional megaloblastic anemia; relation of ascorbic acid and pteroylglutamic acid. 1. Nutritional data and manifestations of animals.* Am. J. Dis. Child., 82, 3, Sept. 1951, 282-309.

Megaloblastic anemia has been produced regularly in monkeys by feeding milk diets deficient in ascorbic acid, the anemia being indistinguishable from that of megaloblastic anemia in humans. It can be cured or prevented by folic or folinic acid without ascorbic acid, or by ascorbic acid alone. It cannot be cured or prevented by vitamin B_{12}. The megaloblastosis is due to a disturbance in the metabolism of folic acid caused by vitamin C deficiency. (Animals which died of the anemia presented only the signs of scurvy and no indications of systemic infection).

PEASE, J. C. AND COOKE, A. M.: *The family doctor and diabetic coma.* Brit. Med. J., Aug. 11, 1951, 336-8.

The essence of this article is to the effect that the family doctor should pass the patient threatened with diabetic coma into the hospital as soon as possible.

111 cases of diabetic acidosis and 74 cases of coma admitted to the Radcliffe Infirmary between 1932-1950 are presented. The prognosis for diabetic precoma is good, while that for coma is bad. All tendencies to "progressive ketosis" should be corrected. Also, every opportunity should be taken

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to teach diabetic patients about the nature of their disease and how to look after themselves when ill.

BRUTON, O. C. AND KANTER, A. J.: *Idiopathic familial hyperlipemia.* Amer. J. Dis. Child., 82, 2, Aug. 1951, 153-159.

Idiopathic familial hyperlipemia is so rare that only 14 cases have been reported, half of them in children. The case presented (a 2-year-old boy) had all the classic findings associated with the condition,—hepatosplenomegaly, xanthoma of the skin, lipemia retinitis, high blood neutral fat level with only slightly elevated phospholipids and cholesterols, absence of other pathological conditions producing hyperlipemia, abdominal crises, decrease in blood fat in a low fat diet and the demonstration of hyperlipemia in other members of his family. It is believed that the large amount of fat in the liver, as demonstrated by biopsy, is the cause of the visceral enlargement and that rapid accumulation of fat in the abdominal viscera could well explain the abdominal crises frequently observed in this disease.

BRANSBY, E. R. AND HAMMOND, W. H.: *Reliability of the clinical assessment of "nutritional state."* Brit. Med. J., Aug. 11, 1951, 330-333.

Examination of children for the estimation of their nutritional condition was undertaken at two different cities, by 3 clinicians in one city and 9 clinicians at the other. A number of children were examined twice and there was, for the same clinician, considerable disagreement in the findings of the two examinations. However, comparison of the clinical assessments made by those clinicians who took part in both trials and the assessment by the different clinicians of different groups of children shows that the clinicians maintained their standards relative to one another and that they could distinguish between groups and generally agree on the order of the differences. If the clinical signs associated with nutritional differences could be made *more objective*, they could be used separately for grading purposes.

DURANT, T. M.: *Nutritional factors in cardiac disease.* Ann. Int. Med., 35, 2, 397-408.

Nutritional inadequacy may occur in congestive failure because the patient can't afford a good diet, because his appetite fails because of anxiety, congestion of the stomach, or gastric irritation by digitalis or diuretics. (In hyperthyroidism, failure may be due to increased metabolism with unsatisfied, increased food requirements). General inanition may result with reduced basal metabolism and reduced total energy metabolism. Under such conditions rest may be helpful. In hypertension, reduced nutrition and salt deprivation may be beneficial. Hypoproteinemia and nutritional anemia, should they develop, are more serious, and impairment of hepatic function usually helps to produce these conditions. Deficiency of thiamin is especially important in cardiac patients, although true beriberi in America occurs chiefly in alcoholics. One of the goals of therapy is the re-establishment of appetite, chiefly by B complex, with emphasis on nicotinamide. Salt substitutes are important. Cation exchange resins permit more real salt in the diet. Intravenous salt-free albumin may be desirable. The effects of long-standing deficiency may be so severe as to defy all attempts at correction. The total fat intake, both vegetable and animal, should be restricted.

BAUMAN, L., CANDELA, J. L. R. AND MARTINO, T.: *Prolonged regulation of alloxan diabetes in dogs.* Ann. Int. Med., 35, 2, Aug. 1951, 391-6.

The response of dogs to alloxan injection is variable. Some develop diabetes after 65 mg. per kilo; others are resistant to doses of 125 mg. per kilo, while a third group suffers a transitory insulin deficiency. Carefully regulated alloxan diabetic dogs can be maintained in perfect health over long periods of time without developing any evidence of ocular or arterial disease.

MAYER, J.: *Problems of tropical nutrition.* Nutrition Rev., 9, 8, Aug. 1951, 225-8.

The general trend of this article by Mayer is to show that malnutrition, and infection, and infestation, are all so common in the tropics that combined effects of the three factors often present themselves as a disease, *sui generis*, in which, for the present, there is no sure way to be certain of the pathogenesis. Nevertheless, it appears to be Mayer's belief that malnutrition plays a bigger role in tropical diseases than is realized at present. Colonizers, by eradicating some bacterial and parasitic diseases, have eliminated an unpleasant but effective form of population control. The inference seems to be that more people are thus spared to feed off the insufficient food supply. Food supply, under colonizing conditions, is rendered still more inadequate by soil erosion resulting from commercial deforestation. In southern Africa we see the most glaring examples of concomitant wasting of both lands and peoples; where a diet of inadequate starchy foods, such as corn, has produced an explosive increase in malnutrition.

In the tropics there are syndromes essentially of dietary origin, such as beriberi, phrynoderma, certain ocular conditions and Kwashiorkor. There are some which are probably of nutritional origin, e.g., tropical ulcer, tropical pernicious anemia, forms of pregnancy anemia, tropical sprue and certain urolithiases. There are others in which dietary factors are extremely important, but which are not ordinarily thought of as nutritional disease, e.g., primary liver cancer and certain forms of pancreatic fibrosis. Finally, there are diseases in which nutritional factors are implicated, e.g., in response to malaria, or secondarily as a result of impaired intestinal absorption as in ankylostominsis and helminthiasis.

Kwashiorkor is probably due to multiple deficiencies, some cases being reversible and those which are not being known as "malignant malnutrition." The disease always is associated with the "plantation diet" of plantains, cassava, sweet potatoes, millet, corn and ground nuts, with the "pap" gruel of guinea corn, the most important staple in the diet of small children.

In the Bantus working in South African mines, liver carcinoma accounts for 90 percent of all cancers.

BOOK REVIEWS

BODY, MIND AND SUGAR. E. M. Abrahamson, M. D. and A. W. Pezet. Henry Holt and Co., New York, 1951, $2.95.

This book, while apparently written for the general public, will prove unusually interesting to the internist and general practitioner. The significance of low blood sugar and hyperinsulinism, first called to our attention by Seale Harris and more recently expanded by Sidney Portis and others, is herein carried considerably further. The 6-hour glucose tolerance test is shown to be essential in detecting hyperinsulinism whether produced by insuloma or by dietary habits. One is inclined to agree with the majority of the authors' assertions, although the value of their special diet in maintaining a normal blood sugar, especially its alleged benefits in asthma and rheumatoid arthritis, will require wider investigation before acceptance. Our suggestion is that the reader obtain the book. If all that it says is true, the authors have made a contribution to human nutrition of great importance.

TEXTBOOK OF ROENTGENOLOGICAL DIFFERENTIAL DIAGNOSIS. (LEHRBUCH DER ROENTGENOLOGISCHEN DIFFERENTIAL DIAGNOSTIK). Teschendorf, Werner. Vol. 1. Diseases of the chest. 780 pages, 865 illustrations. Second edition, Georg Thieme, Stuttgart. Grune & Stratton, New York. $20.20.

This is the first volume of an elaborate textbook on roentgenological diagnosis. Teschendorf has used a new approach in dealing with his material by taking the leading roentgenological signs to discuss the findings and their evaluation for the final diagnosis. In the section on chest pathology we

find chapters on dense shadows of one part of the chest, such as shadows of the pleura, of parts of the lungs, of interlobar spaces, sharply defined and unsharply defined shadows. The differential diagnosis of small patches and larger ones, and the cavities in the lungs are special chapters. One part is devoted to the hilar region, one to the mediastinum.

Chapters are devoted to the size, shape and position of definite parts of the heart. The kymogram and its value for the diagnosis is discussed. Other chapters deal with electrocardiography and its relationship to roentgenology. Very interesting are the chapters on the demonstration of calcified coronary arteries and the calcification of the valves of the heart. For the roentgenological heart function the following tests are discussed: 1. the determination of the heart volume, 2. the kymogram, 3. tests by Abreu, 4. tests by Buerger.

The last two parts concern the examination of the esophagus and the diaphragm. The pathological condition of both organs is discussed. The entire book has 865 illustrations, all of them excellent reproductions, more illustrations than pages. This is a great asset, especially for those readers who are not fully masters of the German language. All modern methods, such as kymography and tomography, are widely used and their importance in the diagnosis is stressed.

The literature is printed at the bottom of each page and covers the entire world. Especially well represented is the work done in the USA. The print is excellent and the publishers can be highly praised for the print, and paper used in their work. Considering that a great deal of the original material has been lost, we want to congratulate Dr. Teschendorf for presenting his subject so well. This book can be highly recommended to all those who are interested in internal medicine and its roentgenological problems.

Franz J. Lust

STUDIES OF UNDERNUTRITION, WUPPERTAL 1946-9. Special Report Series, Medical Research Council, No. 275, by Members of the Dept. of Experimental Medicine, Cambridge, and Associated Workers. His Majesty's Stationery Office, London, Eng., 1951, 12s, 6d.

Here are more than 400 pages of condensed reports on various aspects of malnutrition, including hunger edema, the effects of undernutrition on the skin, radiological observations on the alimentary tract, hepatic structure and function, enlargement of the parotid glands, the neuromuscular system, emotional disturbances and behavioral reactions, the effects of undernutrition and posture on the volume and composition of the body fluids, aspects of renal function and water metabolism, serological responses to antigenic stimuli, the enzyme activity of the red blood cells, sedimentation rates, the excretion of diastase in the urine of undernourished persons, radiological observations of the bones, the response to unlimited food, the volume and composition of human milk, and several other subjects as well. The nucleus of the work was "Studies of Undernutrition, undertaken at Wuppertal 1946-1949." The work is too voluminous to be minutely reviewed, but everyone interested in undernutrition should obtain a copy.

SUMMARY OF "LES HEXOSEMONOPHOSPHATES, LES TRIOSEPHOSPHATES ET L'ACIDE PYRUVIQUE." "LEUR ÉTUDE DANS LE SANG DES SUJETS NORMAUX ET DIABÉTIQUES." Paul Nepveux, M. D., La Ruche, Paris, 1951.

The average quantities of hexosemonophosphates (HMP), triosephosphates (TP) and pyruvic acid (PA) have been determined by a method derived from Cori and Cori's technique in the venous blood of twenty-five normal, thirty diabetic subjects and twelve individuals in a state of diabetic coma.

1. It is possible to get an evaluation of the intensity of phosphorylation, which controls the entry of glucose into metabolism, by comparing the amount of HMP with that of glucose.

2. The HMP and TP in blood are localized in erythrocytes and are apparently combined with potassium, whilst PA is equally distributed in red blood cells and plasma.

3. The amount of HMP in blood varied but little even in the exceptional circumstances brought about by diabetic coma, as shown by the following recorded averages:

in normal fasting subjects	0,131 g. p.1000
in diabetic fasting subjects	0,144 g. p.1000
in subjects during coma	0,119 g. p.1000

TP expressed in terms of quantity of phosphorus contained in the blood of normal fasting subjects averaged 0,017 g. p.1000. In diabetic fasting subjects the figures were also 0,017 g. p.1000.

Pyruvic acid in blood averaged 0,009 g. p.1000 in normal fasting subjects and 0,010 g. p.1000 in diabetics.

4. *Action of insulin* (12 Units of ordinary insulin I.V)

a. The quantity of HMP increased in normal subjects and showed a tendency to decrease in diabetics. This difference is a major characteristic of the disturbance in carbohydrate metabolism. This is probably due less to a deficiency in phosphorylation in diabetics than to a more rapid consumption of the HMP formed.

b. The quantity of TP remained at the same level or increased and these variations as well as those of PA are of the same order in diabetic and in normal subjects.

5. *Under the influence of an oversupply of glucose administered per os*:

a. The quantity of HMP showed very irregular variations in normal as well as in diabetic subjects, which seems to be evidence for the fact that the amount of glucose has little influence on the stimulation of phosphorylation.

b. The quantity of TP remained at the same level or increased in normal as well as in diabetic subjects. This response, identical with that obtained after the insulin injection, makes it possible for us to consider the TP as regulators reacting against any disturbance of carbohydrate metabolism.

c. The PA increased in normal as well as in diabetic subjects.

6. *During the course of diabetic coma* the amounts of HMP and TP remained equivalent to those found in non-comatose diabetics. The treatment provoked a temporary increase of these two metabolites. On the contrary, hyperpyruvicemy was to be observed in the course of coma and stood as evidence of the prominent part played by oxido-reduction processes in carbohydrate metabolism.

MANAGEMENT OF CELIAC DISEASE. Sidney V. Haas, M. D. and Merrill P. Haas, M. D., 188 pages, J. B. Lippincott Company, Philadelphia, Pa. 1951.

Dr. Haas and his son, Merrill, have formulated a hypothesis of the etiology of celiac disease, based on their own experience. Their hypothesis is that there is some mechanism in the intestinal tract of the celiac sufferer which converts polysaccharides into substances that are irritating to the intestinal tract. When all carbohydrates except those present in fruits, vegetables and protein milk are withdrawn from the diet, the diarrhea disappears and nutrition improves. If, however, during the period of normal intestinal activity and nutrition that soon follows the institution of the proper diet, the patient ingests even a small amount of bread, cookie, cake, candy, syrup, plain milk, potato, or any other food containing polysaccharides, a loose or watery stool will occur within from 6 to 18 hours.

Although specimen diets do not seem to be included, that used by Dr. Haas is one which excludes polysaccharides and permits proteins, protein-milk, fruits and "some" vegetables and a reasonable amount of fats. Under such a regime fats appear to be well digested. No doubt the present volume, while convincingly and logically written, will meet with considerable criticism from those pediatrists and gastroenterologists who have formed other conceptions of the disease.

AMER. JOUR. DIG. DIS.

GENERAL ABSTRACTS

KING, W. E., MOTTERAM, R., WEIDEN, S., AND WOOD, I. J.: *Chronic non-suppurative hepatitis; some observations with special reference to diagnosis, management and prognosis.* Med. J. Australia, 1949, 36, 15, 532-536.

During the 3 years in which 14 cases of chronic hepatitis were being studied, no fewer than 7 of them died from liver failure, usually following hematemesis or superimposed acute infection. Ascites was always of serious import. The chemical tests favored by the authors are—albumin-globulin ratio, cephalin flocculation, alkaline phosphatase, and the serum bilirubin test. Liver failure should be treated by the intravenous administration of glucose-saline, serum and blood as indicated. Those who died had had the disease for from 8 months to 5 years.

HOFFBAUER, F. W.: *Bedside diagnosis of jaundice.* Northwest Med., 1949, 48, 11, 757-761.

The correct interpretations of signs observable at the patient's bedside may settle the diagnosis in many difficult cases of jaundice. The sclera must be viewed in a good light if minimal jaundice is to be detected. The barium strip test of Hawkins, Watson and Turner (J. A. M. A., 1945, 129, 514-515) or the button test of Franklin (J. Lab. & Clin. Med., 1949, 35, 1145-1150) are actually bedside methods for detecting bilirubin in the urine. Anorexia at the onset of virus hepatitis is of diagnostic importance. In severe cases of hepatitis, the fetor hepaticus may be noted,—an aromatic, amine odor, often smelled in patients with diffuse liver necrosis. It has an unfavorable prognostic significance, but it may be mimicked by the administration of pure methionine therapeutically. Cirrhosis may be indicated by splenomegaly, ascites, spider nevi, palmar erythema, gynecomastia and an absence of the axillary and pectoral hair. Sometimes a distended gall bladder can be better seen than felt, and it always is significant.

SHLAER, W. H., STEIGMANN, F., FELDMAN, D. AND GOLDENBERG, C.: *Two new drugs in the treatment of amebiasis.* Am. Pract. & Dig. Treat., 1, 9, 966-968.

Two new iodine compounds, ethyl-diiodo-cinnamic acid and diiodo-hydro-methylstibasol were tested in 280 cases of amebiasis and the results of treatment checked after 3 and 6 months. When both drugs were used simultaneously, 67 percent of the patients were free from amebas for at least 6 months. Individually used, each drug had a supposedly higher incidence of "recurrence" of amebiasis after the same length of time.

BORDS, E.: *Role of the esophagus in local and systemic disease.* Amer. Pract. & Dig. Treat., 1, 9, 912-915.

Esophagoscopy has been rendered more acceptable to the patient through the use of flexible instruments through which biopsy material may be obtained, and it has been rendered imperative because esophageal disease now is more vulnerable to successful surgical attack than ever before. Atresia, diverticulum, stricture varices and cancer are the chief diseases under consideration in which better diagnosis is essential to satisfactory surgical approach.

SELESNICK, S.: *Psychotherapy in chronic peptic ulcer.* Gastroenterology, 14, 3, 364-368.

The author found that a group of thirty patients with duodenal ulcer treated by psychotherapy without any regular medical treatment did at least as well as a control group on regular medical therapy for ulcer. No doubt, as he states, properly applied psychotherapy ought to be added to the regular medical treatment in these cases. Unfortunately, no x-ray check was made to determine the degree of healing, and results were based on symptoms or freedom from symptoms. Among the 29 patients on the psychotherapeutic regimen who recovered, 3 failed to attend any group therapy sessions. In such cases, it was assumed that the psychotherapeutic stimulus for a remission was provided by the sympathetic and protective atmosphere of the hospital.

METZGER, H. N.: *The post-cholecystectomy syndrome.* Med. Times, 78, 4, 157-162.

If one makes an erroneous pre-operative diagnosis, removing a stoneless gall bladder does no good, and trouble after operation, in any case, may be expected if one overlooks co-existing stones in the ducts, stricture of the common duct or cystic duct, adhesions involving the duodenum or if there is much hepatitis or pancreatitis. Biliary dyskinesia depending upon spasm of the sphincter of Oddi may be later relieved by making an anastomosis between the dilated common duct and the duodenum or temporized with by means of bland diets and alkalis. Nitroglycerine Gr. 1/100 may terminate an attack suddenly and serves to confirm the functional nature of the attack.

ABBASY, A. S. AND HANAFY, M. M.: *Acute alimentary toxicosis.* Arch. Ped., 67, 8, Aug. 1950, 347-353.

A series of 105 selected cases of acute alimentary toxicosis were divided into 5 groups. Groups I and II were given sulfathiazol and sulfadiazine respectively. Group III was given streptomycin parenterally while Group IV was given streptomycin by mouth. Group V received both streptomycin and sulfadiazine orally. The case death rate in the whole series was 16.2 per cent. Oral streptomycin cut the death rate to 11 per cent while streptomycin with sulfadiazine reduced the death rate to zero. Cases with severe wasting, marked dehydration, shock or pronounced symptoms have a narrow chance of survival.

FINNEY, J. M. R. Jr.: *Some pertinent factors in cholelithiasis,* Rev. Gastroent., 17, 9, 737-755.

Finney is chronically suspicious of all gallstones, silent or otherwise, and believes they should be removed with the gall bladder which contains them at the earliest possible time. To this general rule he makes few exceptions. Following operation he returns the case to the internist to ensure proper follow-up. In discussing the paper, Wangensteen had no profound convictions but was somewhat opposed to Finney's dicta, because gall stone operations so often produced hernia and stricture. He suggested that the formation of gall stones should be more intensively studied.

GRAY, H. K.: *Surgical treatment of benign gastric and duodenal ulcers,* Texas State J. Med., 46, 11, Nov. 1950.

The usefulness of surgery in ulcer therapy ought not to be condemned by the poor results obtained in a very small majority of cases. A gastric ulcer should be considered potentially malignant and, in most instances, operation should be advised. In an uncomplicated duodenal ulcer, surgery is never urgent. Where obstruction or bleeding is present the case must be individualized before resorting to surgery, but repeated hemorrhage usually indicates surgery. In gastric ulcer either excision of the lesion or subtotal gastrectomy is advisable. In duodenal ulcer in a very young person with high values for acid and without complications, the ulcer may be excised. In older patients with lower acid values, gastroenterostomy may be best. Vagus resection cannot be recommended except for marginal ulcer. Medical management of duodenal ulcer has greatly improved, and thus the number of patients who are favorable candidates for surgery has decreased.

HIGHTOWER, N. C., MORLACK, C. G., AND CRAIG, W. M.: *The effect of sympathectomy on the clinical course of peptic ulcer.* Proc. Staff Meet. Mayo Clin., 25, 23, Nov. 8, 1950.

The records of 963 cases in which sympathectomy was done were reviewed, and among them 21 cases of peptic ulcer were found. In 7 cases, symptoms of peptic ulcer developed for the first time following the sympathectomy. In the other 14 cases, peptic ulcer existed prior to the operation. Following sympathectomy in these 14 cases, the symptoms of peptic ulcer became more severe in 3, they remained unaltered in 8, and they became less severe or disappeared in 3. Sympa-

thectomy, as carried out in these cases, did not appear to influence the course of peptic ulcer.

COLLINS, E. N.: *The treatment of peptic ulcer.* Cleveland Clinic Quarterly, 17, 3, 129-140.

100 cases having bilateral vagotomies combined with gastroenterostomies or pyloroplasties for complicated duodenal ulcer have had better results than a comparable series subjected to conventional surgery. The mortality rate was 1 percent. One patient, whose vagotomy was incomplete, developed a jejunal ulcer with obstruction. Otherwise no patient in this series has developed roentgen evidence of recurrent ulcer over a 2 year period of follow-up.

In 20 patients with complicated duodenal ulcer the use of Banthine has produced satisfactory results without surgery, but longer observation is needed.

MANFREDI, D. H.: *Omental segmental infarction in infancy.* Arch. Ped., 67, 5, 247-249.

A child of 9 with abdominal pain, distention and tenderness at McBurney's point was diagnosed as acute appendicitis and opened up. The cause of the pain was infarction in the omentum which produced a tumor-like mass 2 by 3 centimeters. This was removed and an uneventful recovery occurred. The condition is excessively rare in infants, no other case having been reported in 20 years. The cause is probably a twisting of the omentum.

SHERWOOD, P. M.: *An outbreak of syringe-transmitted hepatitis with jaundice in hospitalized diabetic patients.* Ann. Int. Med., 33, 2, 380-396.

A 44 percent incidence of syringe transmitted hepatitis occurred in a group of hospitalized diabetic patients. The causative agent was transmitted by the multiple-dose-per-syringe technic of administering insulin. The incubation period ranged from 64 days to 106 days and is compatible with that seen in homologous serum jaundice. The precaution of using a fresh, sterile syringe and needle for any injection or blood collection will greatly reduce the hazard of disseminating infected serum from patient to patient.

GROSSMAN, J. W., FISHBACK, C. F. AND LOVELACE, W. R. II.: *Hemorrhage from a Meckel's diverticulum as a cause of melena in infancy.* Radiology, 55, 2, 240-243.

A case is reported of melena caused by bleeding from a Meckel's diverticulum, the latter demonstrated by x-ray. Surgical removal of the diverticulum resulted in cessation of the melena and complete recovery of the patient.

DORFMAN, M.: *Carcinoma associated with diaphragmatic herniation of the stomach.* Radiology, 55, 2, 254-256.

Dorfman adds one more case to the 35 examples in the literature of carcinoma associated with diaphragmatic herniation of the stomach. A portion of the stomach was herniated through the esophageal hiatus, the esophagus was of normal length, and the herniated portion of the stomach presented an irregular filling defect with virtual absence of the normal mucosal pattern at this site. The stomach was removed, followed by an esophagojejunostomy. He died on the fourth postoperative day. Examination of the stomach showed primary carcinoma. The patient had had attacks of angina pectoris for several years.

FELDMAN, M.: *Perforation of peptic ulcer.* Radiology, 55, 2, 217-222.

Feldman describes the hitherto inadequately described walled-off perforations. Perforation most commonly involves the greater peritoneal cavity and those involving the lesser peritoneal cavity have received little attention. Retroperitoneal perforations occasionally occur on the posterior wall of the distal duodenum. Pinpoint perforations are not an uncommon complication in recurrent active duodenal ulcer and, in them, the x-ray examination will reveal a small subphrenic or periduodenal air-pocket, best observed in a spot compression film made with the patient erect, before the gas has absorbed.

GIANTURCO, C.: *Examination of the stomach by "oil contrast."* Radiology, 55, 2, 174-177.

A method for the examination of the gastric mucosa called "oil contrast" is described. This depends upon the administration of 3 ounces of barium followed by 3 ounces of mineral oil. The procedure is particularly useful in those gastric regions which cannot be reached with the compression technique, i.e., the higher portions of the body and fundus.

ALLEN, R. P.: *Cardio-esophageal relaxation.* Radiology, 55, 2, 214-216.

The discovery of 2 new cases of infantile vomiting caused by cardio-esophageal relaxation in the past 6 months, suggests that many of the undiagnosed cases of infantile vomiting may, by proper x-ray examination, be so classified and successfully treated. Absence of intestinal gas was observed in one of these cases, and this may be one of the signs. Keeping the infant in an upright position is adequate treatment. Atropine gr. 1/4000 restored tone to the cardia in a single experiment in one case.

NAYER, H. R.: *Right-sided stomach associated with eventration of the diaphragm simulating hydropneumothorax.* Am. J. Roentgenology and Rad. Therapy, 64, 1, 50-52.

A case is presented with acute pulmonary infection of the right lower lobe whose chest film suggested hydropneumothorax, but a barium meal showed that the appearance of hydropneumothorax was in reality produced by a right-sided stomach with eventration of the right diaphragm. There was no evidence of transposition of other organs. The presence of right-sided stomach as the sole evidence of situs inversus is exceedingly rare.

BROWN, C. L.: *The role of the internist in the detection and early diagnosis of gastric carcinoma.* Radiology, 55, 2, 165-169.

When a patient over 35 years of age complains for the first time of gastric symptoms not readily explainable on some other basis, and not responding to treatment, the internist should suspect cancer of the stomach. Gastric analysis, x-ray, gastroscopy and the study of exfoliative cytology are the available diagnostic methods. The x-ray examination is the most important, being of high accuracy and capable of detecting cancer in more than 90 percent of cases suffering from it.

HODGES, F. J.: *Standard radiologic methods used in the search for gastric tumors.* Radiology, 55, 2, 170-173.

Both fluoroscopy and filming should be used in studying the stomach, since both are of value and complement each other. In fluoroscopy, the radiologist must be "chronically suspicious" that a gastric lesion exists and not terminate the screen examination until he is convinced one way or the other. Radiological examination of the stomach still reigns supreme as the procedure of greatest dependability in the search for gastric lesions, being capable of detecting lesions in about 95 percent of all patients with subsequently proved gastric cancer. Lesions in the upper part of the stomach are more difficult to detect than those lower down and demand acute observation, positioning and the spot-film device.

ARONSTAM, E. M.: *Acute abdominal manifestations of ancylostomiasis.* U. S. Armed Forces M. J., 1, 8, 935-937.

Out of 224 ancylostomiasis patients admitted to Gorgas Hospital (Ancon C. Z.), 21 were placed in the surgical service complaining of abdominal distress of sufficient severity to warrant a tentative diagnosis of an acute abdominal inflammation. Needless surgery is avoided by stool examinations. Elevated eosinophile counts are suggestive of parasitism. The disease may successfully mimic acute appendicitis. The therapeutic test is important also.

ACREE, F. M.: *Amebiasis; its diagnosis and treatment.* J. Arkansas M. S., XLVII, 6, Nov. 1950, 95-98.

Dysentery is a feature of relatively few cases (3.3 percent) of amebic infection. Of 23,000 admissions over a period of 13 years, only 446 (2 percent) were found to have amebic infection. Cyst carriers may show no symptoms or very mild ones. In more active cases, symptoms referable to the G. I. tract and indeed to almost every structure of the body, may occur. Amebic dysentery may follow a milder infection or may come on suddenly. Unless treated it may become chronic and fatal. Diagnosis is based on the demonstration of *E. histolytica* in the stool or ulcer bases. Emetine is preferably limited to acute dysentery and amebic hepatitis. Carbarsone is the most popular of the arsenicals, and is valuable in all forms of the disease. The diet should be low in roughage, fat and carbohydrates. Cure is judged from repeated stool examinations.

NOTES

T. Burwell Robinson is new claims department manager for A. H. Robins Co., Inc., Richmond, Va., after five years on the staff of the Insurance Medical Division of the Veterans Administration. Mr. Robinson, a native of Richmond, is a graduate of the University of Richmond. He was a medical service representative for seven years and during World War II served in the Medical Administrative Corps of the Army.

The A. H. Robins Co., Inc., and its employes took an active part in the recent Community Chest campaign for the Richmond area. For the second consecutive year, employes of the Richmond plant and office showed the highest individual contributor's average in the Industrial Division. Seventy-nine employes contributed $2,755, an average of $34.87, to exceed their quota by 275 percent. The company was the first contributor to the Special Gifts Division. Several executives served as volunteer solicitors. G. Mallory Freeman, advertising manager, wrote and narrated a dramatic feature for the campaign opening.

A seven-week swing around the Caribbean took Dr. Martin Reyes, export manager of the A. H. Robins Co., Inc., to Cuba, the Dominican Republic, Puerto Rico, Venezuela, Central America and Mexico. After conferring with Robins representatives in these Latin American countries, Dr. Reyes returned to the company's home office at Richmond, Va., November 8.

E. F. Heffner, Jr., vice president and general sales manager of the A. H. Robins Co., Inc., Richmond, Va., returned early in November from Montreal, where he conferred with W. J. Hasey, the Canadian division manager, regarding the company's 1952 promotional plans for Canada.

Representatives attending the training school of A. H. Robins Co., Inc., at Richmond, Va., had an opportunity to hear themselves as others hear them at a session where wire recordings were played back and discussed.

To bring out the importance of voice modulation in detail presentations, five representatives read the same copy. The recordings were then compared and discussed.

E. Claiborne Robins, company president, welcomed the visiting representatives to the school, which was in session from October 14 to 26. Attending were 27 men from the Southern, Chicago, Kansas City, West Coast, New England, New York, Pennsylvania, Southwestern and Virginia divisions. Each session was conducted by panel discussions.

Briefing of representatives was conducted by Dr. E. L. Jackson, medical diector; Dr. William R. Bond, clinical director; E. F. Heffner, vice-president in charge of sales; Mallory Freeman, advertising director; Dr. Robert Murphey, research chemist, and others. Discussions were held on company products, including Robitussin, Robalate, Entozyme, Pabalate, Donnatal, Phenaphen, Phenaphen with Codeine and Allbee with C.

WINTHROP-STEARNS STARTS SECTIONAL CONFERENCES

Winthrop-Stearns Inc., has launched a series of annual Fall sectional conferences with a three-day meeting of its Boston, Buffalo and Hartford divisions at Swampscott, Mass., it was recently announced by Joseph G. Noh, vice-president and director of sales.

Objective of the conferences, held in a number of cities across the country and attended by all professional service representatives of the company in each area, is to translate new developments in pharmaceutical research and clinical investigations into more efficient service to physicians, hospitals and pharmacists.

The conferences also include professional service and merchandising plans, presented to the staff by audio-visual technics. Joining Mr. Noh in these presentations at the conferences are Dr. E. J. Foley, medical diector; Dr. Ernst Zander, associate medical director; and Arthur W. Jensen, sales manager.

Emphasis is placed not only on current research and developments at the Sterling-Winthrop Research Institute, but on new applications of already established preparations as reported in medical journals throughout the world. Such applications include those of the radiopaque compound Diodrast in different phases of angiocardiography and cholangiography; of pHisohex in maternity wards to prevent skin infections among infants and its use by the armed forces in treatment of wounds; and of Pontocaine in local anesthesia for certain types of operations.

"MYRIAD" OF THERAPEUTIC USES OF PAPAIN CITED IN MONOGRAPH

A myriad of uses of papain, the protein-digesting enzyme obtained from the tropical papaw or carica papaya fruit, are reported in a monograph just published by the New York Academy of Sciences, which brings together for the first time the results of world-wide investigation of the therapeutic values of papain.

Roy Waldo Miner of the Academy is editor of the monograph, and Dr. Maurice L. Tainter, director of the Sterling-Winthrop Research Institute, is consulting editor.

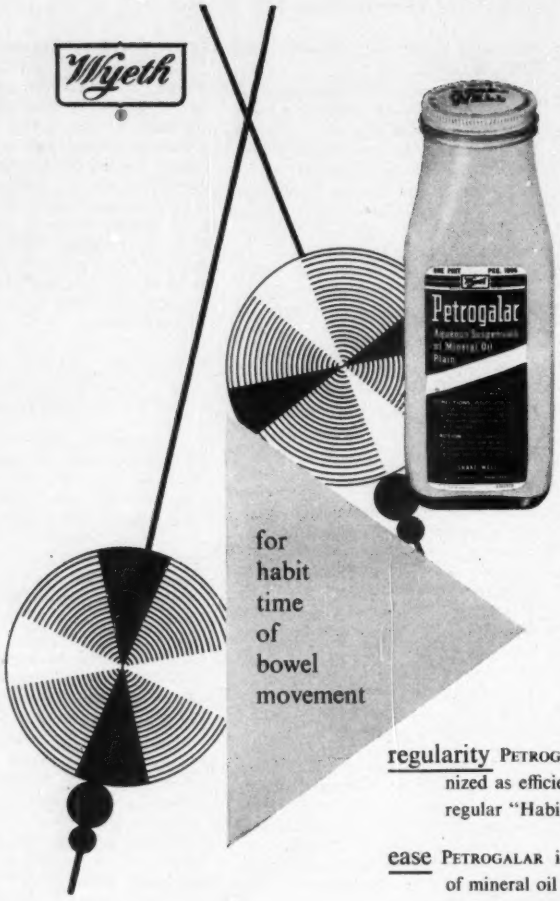
The monograph details the intesified scientific search since 1874 to determine the properties of the substance which has been used for centuries by tropical natives to prevent dyspepsia, to treat wounds and infections, to tenderize meat and for many other purposes.

The monograph contains a review of the literature on present and potential therapeutic significance of papain, prepared by Drs. Kao Hwang ad A. C. Ivy of the department of clinical science, University of Illinois. It is a comprehensive report citing 338 separate investigations.

Other articles prepared by staff members of the Sterling-Winthrop Research Institute, describe studies covering the pharmacology, chemistry, therapeutic activity and other scientific aspects of papain.

"No other plant of the tropics enjoys the popularity and myriad of uses as does the carica papaya," Dr. Tainter explains in the foreword. "Its role as a delicacy in syrups and marmalades is overshadowed by its therapeutic values, considered 'wonderful and myste-

Wyeth



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in gastric hyperacidity

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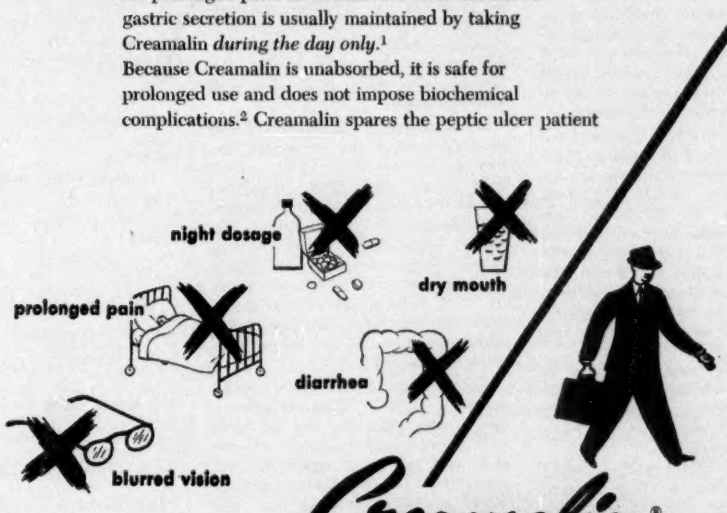

AMORPHOUS ACID SOLUBLE REACTIVE ALUMINUM HYDROXIDE

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1. Breuhaus, H. C., Akre, O. H., and Everly, J. B.: *Gastroenterology,* 16:172, Sept., 1950.
2. Jordan, Sara M.: *Ann. West. Med. & Surg.,* 4:133, Mar., 1950.

rious' in the medical lore of the natives."

Papain's present clinical applications include use as a digestant, antacid and mucosolvent. Its most important property yet discovered, the monograph points out, is its unique, powerful proteolytic activity. Extracted from the milky juice or latex of the big green papaya fruit, the enzyme papain resembles the body's pepsin or trypsin in its digestive action on protein.

For this reason, preparations of it are widely prescribed in cases of gastro-intestinal and biliary disturbances. Its stability and activity over a wide pH range make it superior to animal enzymes for many purposes in pharmaceutical preparations, the monograph explains.

Among preparations commercially available which contain papain are Caroid and Bile Salts Tablets, Alcaroid Antacid Powder and Caroid Dental Powder.

Papain has also been found to have a rapid solvent effect on mucus and an ability to digest sloughing or dead tissues. Reports are cited showing that it has proved useful in dissolving the eschar of burns and the membranes of diphtheria.

In some countries reports have been published of its effectiveness against roundworms and certain intestinal worms which constitute prime causes of economic loss among the peoples in many regions. Various lesions, such as chronic eczema, psoriasis, ulcers of the tongue and throat—even freckles—are reported to have been treated with favorable results by local use of papain.

Considerable research is said to have been conducted to determine its behavior in the peritoneal cavity and possible prevention of post-operative adhesions.

The United States is the world's largest consumer of crude papain, drawing almost 500,000 pounds a year from Ceylon and British Africa, the two chief sources of supply. Increasing applications for a wide variety of industrial as well as medical purposes are reflected in a 55 per cent rise in imports since 1941, the monograph points out.

In addition to its therapeutic uses, papain assists in manufacture of preparations for tenderizing meats in treatment of beer to prevent oxidation and chill hazes, in manufacture of chewing gum and face creams, and in the prevention of wool shrinkage and de-gumming of silk.

Natives collect the papaya latex in such places as the slopes of snow-crested Mt. Kilimanjaro in East Africa. It is obtained by tapping the unripe fruit and is sent here in the form of tan-colored dry granules or powder. New technics are reportedly being developed for obtaining papain from ground leaves. This is expected to make possible yields from plants too young and too old to bear fruit, and from the male plants, which far outnumber the females but are now unproductive of papain.

NEW B COMPLEX PREPARATION INTRODUCED BY WINTHROP-STEARNS

Winthrop-Stearns Inc. has introduced a new injectable vitamin B complex preparation called Betasynplex with Vitamin B12, found highly effective for multiple vitamin therapy in cases of deficiency of B complex factors. The preparation has proved especially useful for patients who fail to respond to oral administration.

In addition to Vitamin B12 the product contains five important factors of vitamin B complex which have been synthesized: thiamine, riboflavin, nicotinamide, calcium pantothenate, and pyridoxine. Vitamin B 12, a highly potent constituent of liver extract, is the liver's principal anti-pernicious anemia factor, and is most effective by injection. It stimulates the production and maturation of red blood cells in the bone marrow.

Betasynplex comes in a stable, instantly soluble Niphanoid form in single dose ampuls and multiple (10 dose) vials. Manner of use is to add two cc of sterile distilled water to a single dose ampul, or 20-30 cc to a 10 dose vial. The solution which forms almost immediately is injected either intramuscularly or intravenously.

Average adult dose is one single ampul daily, but in cases of severe deficiency such as in pellagra, beriberi, ariboflavinosis or pernicious anemia, one or two doses may be injected daily. To increase the vitamin reserve before operations, especially for elderly persons and those on restricted diets because of diabetes, peptic ulcer or epilepsy, one or two injections may be given daily for several days prior to the operation.

NEW THERAPY FOR FUNCTIONAL G. I. DISTRESS

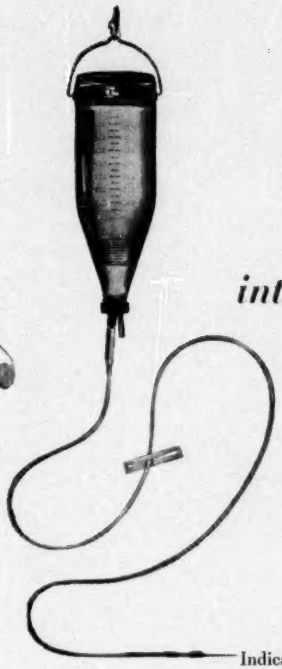
Decholin with Belladonna, manufactured by the Ames Company, Elkhart, Indiana, provides spasmolysis and hydrocholeresis for the management of the prevalent symptom-complex Functional G. I. Distress. Although there are no detectable signs of organic disease in this disorder, patients complain of vague upper abdominal distress, pain, belching, bloating flatulence, capricious appetite and constipation. The therapeutic combination of belladonna with dehydrocholic acid gives these patients relief.

The spasmolytic action of Decholin with Belladonna relieves the pain of smooth muscle spasm, suppresses incoordinate peristaltic waves and facilitates biliary and pancreatic drainage through relaxation of the sphincter of Oddi. Hydrocholeresis with Decholin flushes the biliary tract with a copious flow of thin, free-flowing bile, improves hepatic aterial blood flow and produces mild natural laxation without catharsis.

Decholin with Belladonna is administered in a dosage of one or two tablets three times daily after meals.

INDEX TO ADVERTISERS

Terramycin



intravenous

Indicated for use in all infections of such severity that intravenous injection is the preferred route, Crystalline Terramycin Hydrochloride Intravenous provides a rapid acting form for the attainment of immediate high serum concentrations. Recommended when oral therapy is not feasible, in severe fulminating or necrotizing infections, in surgical prophylaxis in selected cases, and in peritonitis. For hospital use only.

Supplied — *10 cc. vial, 250 mg.;*
20 cc. vial, 500 mg.

Terramycin is also available as *Capsules, Elixir, Oral Drops, Ophthalmic Ointment, Ophthalmic Solution.*

ANTIBIOTIC DIVISION **Pfizer** CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

(The Council on Pharmacy and Chemistry of the American Medical Association has adopted the following statement of Actions and Uses and of Dosage for publication in connection with a description of Banthine Bromide for inclusion in New and Nonofficial Remedies)

METHANTHELINE BROMIDE.—*Banthine® Bromide (Searle)*

β-diethylmethylaminoethyl 9-xanthenecarboxylate bromide

Actions and Uses.—Methantheline bromide, a parasympatholytic agent, produces both the peripheral action of anticholinergic drugs such as atropine and the ganglionic blocking action of drugs such as tetraethylammonium chloride. Tolerated amounts of methantheline bromide exert side effects typical of atropine-like drugs, but cause less tachycardia, and also less postural hypotension than does tetraethylammonium chloride. Toxic doses produce a curare-like action at the somatic neuromuscular junction.

Clinical studies indicate that the drug effectively inhibits motility of the gastrointestinal and genitourinary tracts and, to a variable degree, diminishes the volume of perspiration and salivary, gastric and pancreatic secretions. It also decreases mucoprotein secretion. Like atropine, it produces mydriasis and cycloplegia when applied locally to the eye or administered systemically, but until more clinical evidence becomes available, its local use for this purpose is not recommended. The value of the drug for preventing abnormal cardiac reflexes through the vagus during thoracic surgery, or as an agent for routine preoperative medication in place of atropine, requires further investigation before final conclusions can be reached.

Methantheline bromide is indicated for clinical use whenever anticholinergic spasmolytic action is desired, provided it is not contraindicated because of its atropine-like characteristics or because of a patient's intolerance to the unavoidable side effects of such therapy. It is useful as an adjunct in the management of peptic ulcer, chronic hypertrophic gastritis, certain less specific forms of gastritis, pylorospasm, hyperemesis gravidarum, biliary dyskinesia, acute and chronic pancreatitis, hypermotility of the small intestine not associated with organic change, ileostomies, spastic colon (mucous colitis, irritable bowel), diverticulitis, ureteral and urinary bladder spasm, hyperhidrosis or control of normal sweating which aggravates certain dermatoses, and control of salivation.

Methantheline bromide produces some degree of cycloplegia and mydriasis in therapeutic doses and therefore should not be administered to patients with glaucoma. It sometimes decreases the ability to read fine print. Xerostomia (dryness of the mouth) is a common, sometimes transient, side effect. Urinary retention of varying degree may occur in elderly male patients with prostatic hypertrophy, and some patients may have difficulty emptying the rectum. Patients with edematous duodenal ulceration may experience nausea and vomiting during initial administration of the drug. These patients should take only liquids during the institution of drug therapy. All patients should be advised of the possible occurrence of side effects. Overdosage sufficient to produce a curare-like action may be counteracted by prompt subcutaneous injection of 2 mg. of neostigmine methylsulfate.

Dosage.—Methantheline bromide is administered orally or parenterally by either the intramuscular or intravenous route. Parenteral administration is not advised for patients able to take the drug orally. The average initial adult dose, oral or parenteral, is 50 mg. For patients with considerable intolerance, 25 mg. may be employed. In the management of peptic ulcer, a beginning schedule of 50 mg. three times daily before meals and 100 to 150 mg. on retiring is suggested. However, the usual effective dose is 100 mg. four times daily, although some patients may require more or less than this amount. The dosage may be increased to tolerance, using dryness of the mouth as a guide, and adjusted to meet the individual response of patients. Maintenance dosage in peptic ulcer is usually considered to be about one-half the therapeutic level. In the management of other hypermotile or hypersecretory states, the dosage should be adjusted to the smallest amount which will relieve the symptoms. When spastic conditions are secondary to inflammatory or other organic lesions, therapy directed toward the cause should be employed whenever possible.

G. D. SEARLE & CO.
Tablets Banthine Bromide: 50 mg.
Ampuls Banthine Bromide: 50 mg.